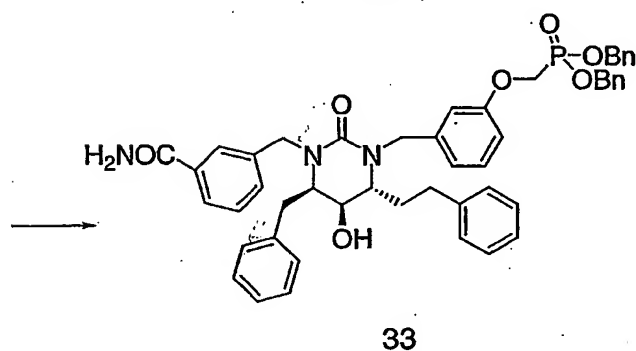
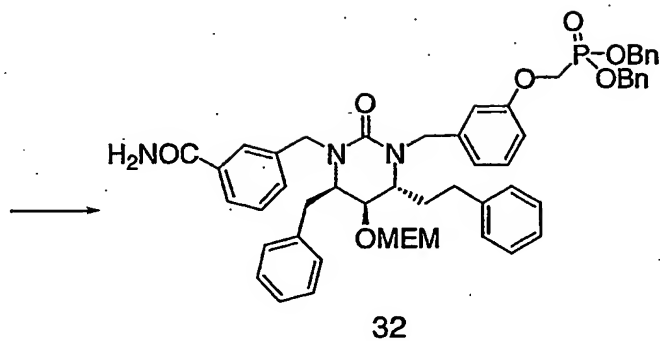


## Scheme 4 (continued)



### Example Section C

#### Example 1

Scheme 1 : Example, {4-[1,3-Bis-(3-carbamoyl-benzyl)-5-hydroxy-2-oxo-6-phenethyl-hexahydro-pyrimidin-4-ylmethyl]-phenoxy-methyl}-phosphonic acid dibenzyl ester (6)

Commercially available Z-D-Tyr(TBU)-OH 1 is converted to the tetrahydropyrimidine 2 using the same procedures reported by De Lucca for conversion of Z-Phe into the analogous tetrahydropyrimidinone (J. Med. Chem. 1997, 40, 1707-1719). Bis-alkylation by treatment with excess m-cyanobenzylbromide affords the disubstituted urea 3 (J. Med. Chem. 1997, 40, 1707-1719). Removal of the MEM group and the t-butyl ether using standard conditions e.g. TFA (Green) affords the diol 4. Treatment of the diol 4 with hydrogen peroxide in DMSO affords the carboxamide 5. Alkylation of 5 with trifluoro-methanesulfonic acid bis-benzyloxy-phosphorylmethyl ester in the presence of base (e.g. cesium carbonate) affords the dibenzyl phosphonate 6.

The meta analog, {3-[1,3-Bis-(3-carbamoyl-benzyl)-5-hydroxy-2-oxo-6-phenethyl-hexahydro-pyrimidin-4-ylmethyl]-phenoxy-methyl}-phosphonic acid dibenzyl ester and para analog, {2-[1,3-Bis-(3-carbamoyl-benzyl)-5-hydroxy-2-oxo-6-phenethyl-hexahydro-pyrimidin-4-ylmethyl]-phenoxy-methyl}-phosphonic acid dibenzyl ester are prepared using Scheme 1 except substituting Z-D-m-Tyr(TBU)-OH and Z-D-o-Tyr(TBU)-OH for Z-D-Tyr(TBU)-OH respectively. The Z-D-m-Tyr(TBU)-OH and Z-D-o-Tyr(TBU)-OH amino acids are prepared from the unprotectd amino acids. Thus, D-m-Tyr-OH and D-o-Tyr-OH (see Abbott scheme 1) are treated with dibenzyl dicarbonate in the presence of base e.g. triethylamine to afford the Z-D-m-Tyr-OH and Z-D-o-Tyr-OH protected amino acids respectively. Further treatment of Z-D-m-Tyr-OH and Z-D-o-Tyr-OH with t-butyl chloride in the presence of base e.g. pyridine affords the Z-D-m-Tyr(TBU)-OH and Z-D-o-Tyr(TBU)-OH amino acids respectively (Green).

#### Example 2

Scheme 2 : Example, (4-{2-[6-Benzyl-1,3-bis-(3-carbamoyl-benzyl)-5-(2-methoxy-ethoxymethoxy)-2-oxo-hexahydro-pyrimidin-4-yl]-ethyl}-phenoxy-methyl)-phosphonic acid dibenzyl ester (13)



Boc-Phe 7 is converted to the allylic alcohol 8 using the same procedures reported by De Lucca et al. for the conversion of Z-Phe to the corresponding Z- allylic alcohol (J. Med. Chem. 1997, 40, 1707-1719). The allylic alcohol 8 is reacted with 4-methoxybenzylmagnesium chloride to afford the alkene 9 (J. Med. Chem. 1997, 40, 1707-1719). The 4-methoxybenzylmagnesium chloride is prepared from 4-methoxybenzylchloride according to the procedure of Van Campen et al. (J. Amer. Chem. Soc. 1948, 70 p2296). The alkene 9 is converted to the tetrahydropyrimidinone 10 using the same series of procedures reported by De Lucca et al. (J. Med. Chem. 1997, 40, 1707-1719). Treatment of the nitrile 10 with hydrogen peroxide in DMSO affords the carboxamide 11 (Synthesis, 1989, 949-950). The carboxamide 11 is treated with trimethylsilylbromide to form the phenol 12 (Green) which is then alkylated with trifluoro-methanesulfonic acid bis-benzyloxy-phosphorylmethyl ester in the presence of base (e.g. cesium carbonate) to yield the dibenzyl phosphonate 13.

15 The ortho, (2-{2-[6-Benzyl-1,3-bis-(3-carbamoyl-benzyl)-5-(2-methoxy-ethoxymethoxy)-2-oxo-hexahydro-pyrimidin-4-yl]-ethyl}-phenoxy-methyl)-phosphonic acid dibenzyl ester and meta, (3-{2-[6-Benzyl-1,3-bis-(3-carbamoyl-benzyl)-5-(2-methoxy-ethoxymethoxy)-2-oxo-hexahydro-pyrimidin-4-yl]-ethyl}-phenoxy-methyl)-phosphonic acid dibenzyl ester analogs, are prepared using the same procedures reported in Scheme 2 except 4-methoxybenzylmagnesium chloride is replaced with 2-methoxybenzylmagnesium chloride and 3-methoxybenzylmagnesium chloride respectively. The grignard reagents are prepared from commercially available benzyl chlorides using the procedure of Van Campen et al. (J. Amer. Chem. Soc. 1948, 70 p2296).

### 25 Example 3

Scheme 3 : Example, {3-[6-Benzyl-3-(3-carbamoyl-benzyl)-5-hydroxy-2-oxo-4-phenethyl-tetrahydro-pyrimidin-1-ylmethyl]-phenoxy-methyl}-phosphonic acid dibenzyl ester (24).

Boc-Phe 7 is converted into the azide 14 using the same procedures reported by De Lucca et al. for the conversion of CBZ-Phe into the analogous CBZ azide (J. Med. Chem. 1997, 40, 1707-1719). Catalytic hydrogenolysis of the azide affords the amine 15 (J. Med. Chem. 1997, 40, 1707-1719). Reductive amination of the amine with 3-cyanobenzaldehyde (US 6313110)

affords the secondary amine 16. Treatment with 4N HCl affords the primary amine 17 (Green). Reductive amination with 3-benzyloxybenzaldehyde affords the benzyl ether 18 (US 6313110). Treatment of the benzyl ether 18 with MEM-chloride in the presence of base (e.g. DIEA) forms the MEM protected product 19 (J. Med. Chem. 1997, 40, 1707-1719).

- 5 Treatment of diamine 19 with CDI affords the tetrahydropyrimidinone 20. Treatment of the nitrile 20 with DMSO and hydrogen peroxide (Synthesis 1989, 949-950) affords the carboxamide 21. Catalytic hydrogenolysis affords the phenol 22 (Green) which is then alkylated with trifluoro-methanesulfonic acid bis-benzyloxy-phosphorylmethyl ester in the presence of base (e.g. cesium carbonate) to yield the dibenzyl phosphonate 23. Removal of  
10 the MEM group using trifluoroacetic acid affords the product 24 (Green).

- The ortho {2-[6-Benzyl-3-(3-carbamoyl-benzyl)-5-hydroxy-2-oxo-4-phenethyl-tetrahydro-pyrimidin-1-ylmethyl]-phenoxy-methyl}-phosphonic acid dibenzyl ester. and para, {4-[6-Benzyl-3-(3-carbamoyl-benzyl)-5-hydroxy-2-oxo-4-phenethyl-tetrahydro-pyrimidin-1-ylmethyl]-phenoxy-methyl}-phosphonic acid dibenzyl ester are prepared using the same  
15 procedures reported in Scheme 3 except substituting 3-benzyloxybenzaldehyde with 2-benzyloxybenzaldehyde and 4-benzyloxybenzaldehyde respectively.

#### Example 4

- 20 Scheme 4 : Example, {3-[4-Benzyl-3-(3-carbamoyl-benzyl)-5-hydroxy-2-oxo-6-phenethyl-tetrahydro-pyrimidin-1-ylmethyl]-phenoxy-methyl}-phosphonic acid dibenzyl ester (33)

- The amine 15 (Scheme 3) is transformed to the secondary amine 25 through reductive amination with 3-benzyloxybenzaldehyde (US 6313110). Treatment of BOC-amine 25 with  
25 trifluoroacetic acid releases the primary amine 26 (Green) which is then subjected to a second reductive amination with 3-cyanobenzaldehyde to afford the bis-substituted amine 27 (US 6313110). Treatment of the benzyl ether 27 with MEM-chloride in the presence of base (e.g. DIEA) forms the MEM protected product 28 (J. Med. Chem. 1997, 40, 1707-1719). Treatment of diamine 28 with CDI affords the tetrahydropyrimidinone 29. Treatment of the  
30 nitrile 29 with DMSO and hydrogen peroxide (Synthesis 1989, 949-950) affords the carboxamide 30. Catalytic hydrogenolysis affords the phenol 31 (Green) which is then alkylated with trifluoro-methanesulfonic acid bis-benzyloxy-phosphorylmethyl ester in the

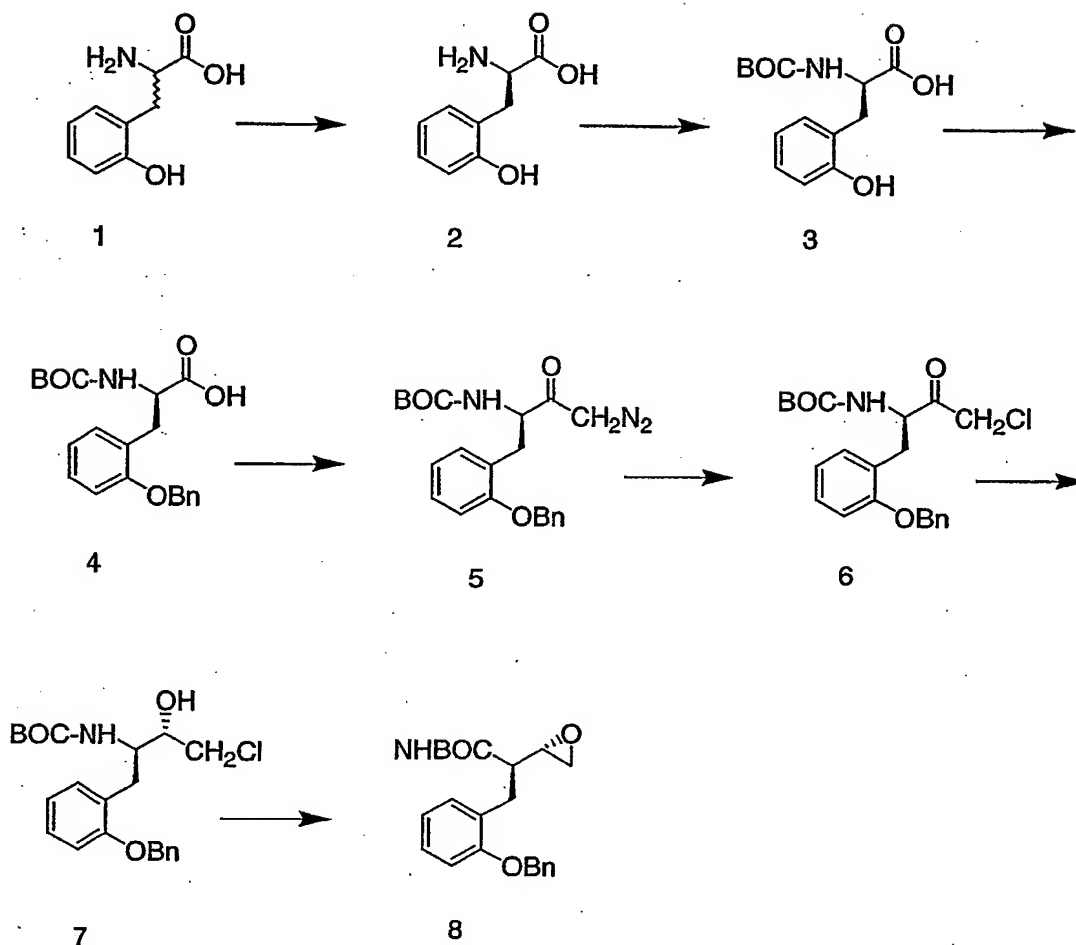
presence of base (e.g. cesium carbonate) to yield the dibenzyl phosphonate 32. Removal of the MEM group using trifluoroacetic acid affords the product 33 (Green).

Example 5

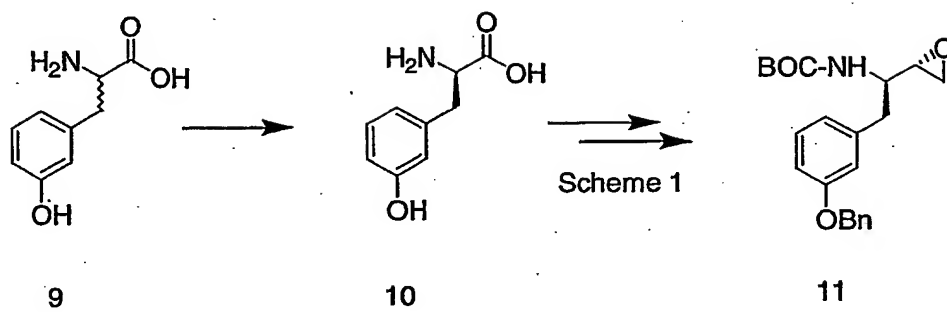
- 5 Ortho analog, {2-[4-Benzyl-3-(3-carbamoyl-benzyl)-5-hydroxy-2-oxo-6-phenethyl-tetrahydro-pyrimidin-1-ylmethyl]-phenoxy-methyl}-phosphonic acid dibenzyl ester and para analog, {4-[4-Benzyl-3-(3-carbamoyl-benzyl)-5-hydroxy-2-oxo-6-phenethyl-tetrahydro-pyrimidin-1-ylmethyl]-phenoxy-methyl}-phosphonic acid dibenzyl ester are prepared using Scheme 4 except replacing 3-benzyloxybenzaldehyde with 2- benzyloxybenzaldehyde and 4-  
10 benzyloxybenzaldehydes respectively.

**Scheme Section D**

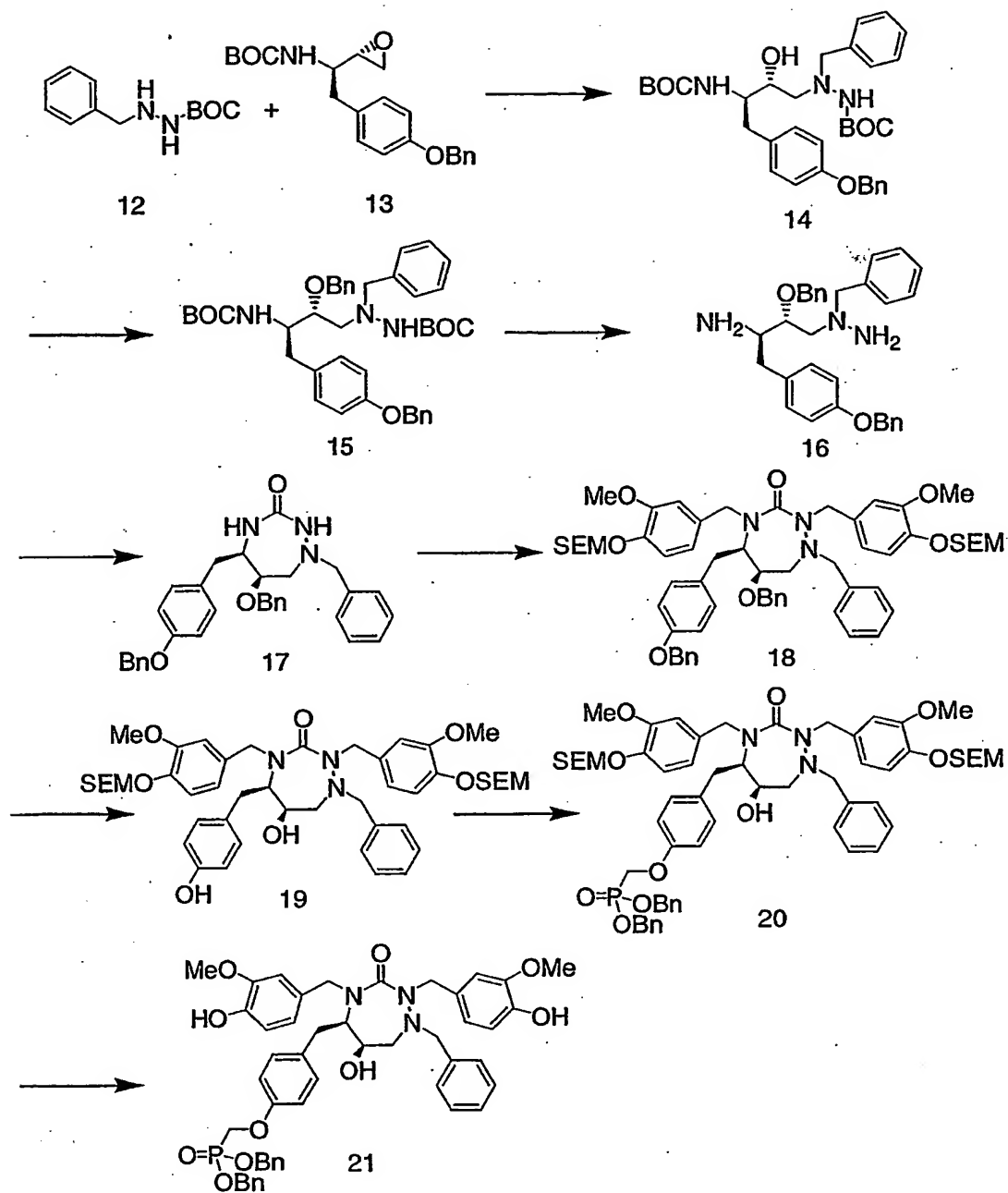
Schemes 1-6 are described in the examples.

**Scheme 1**

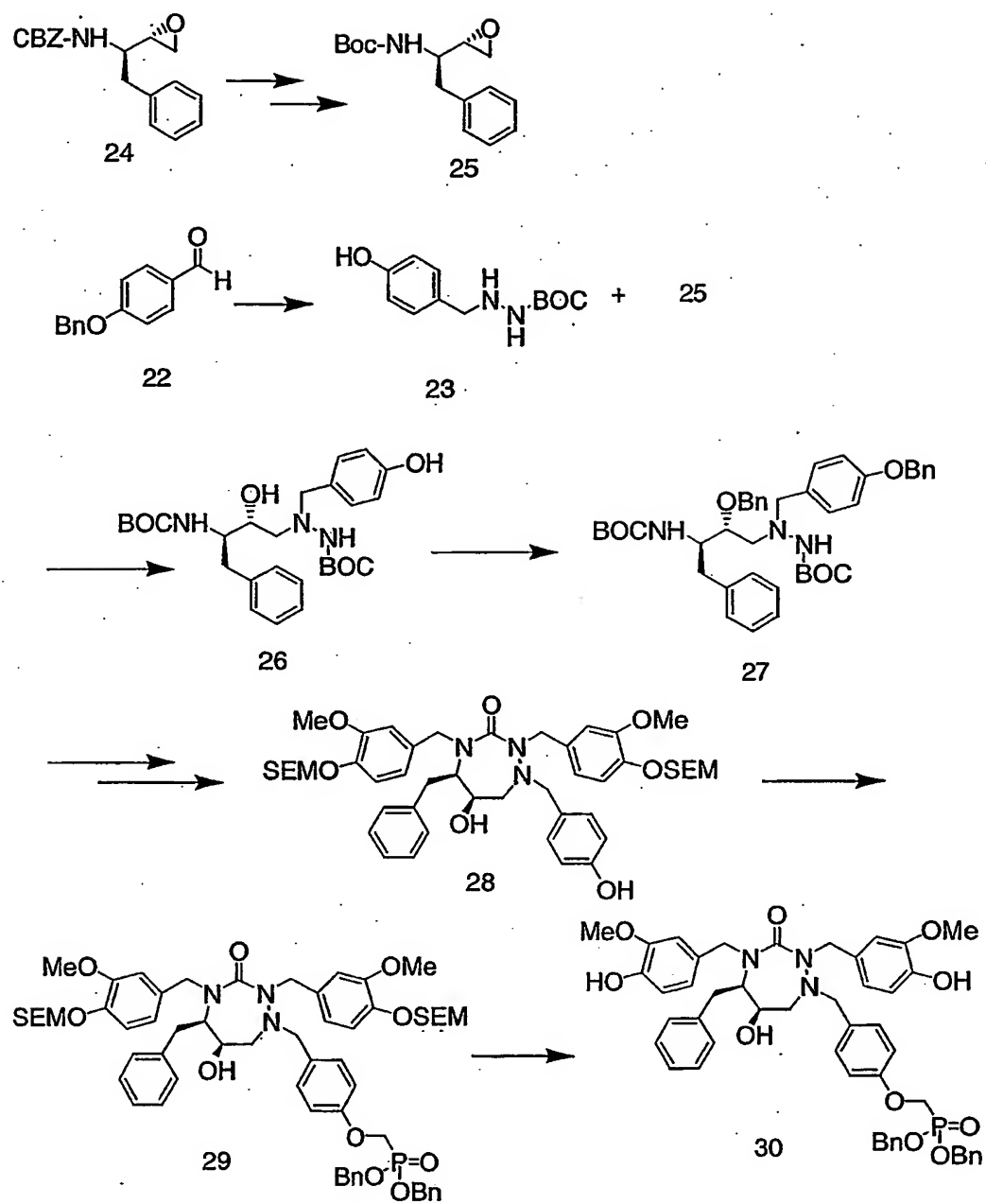
## Scheme 2



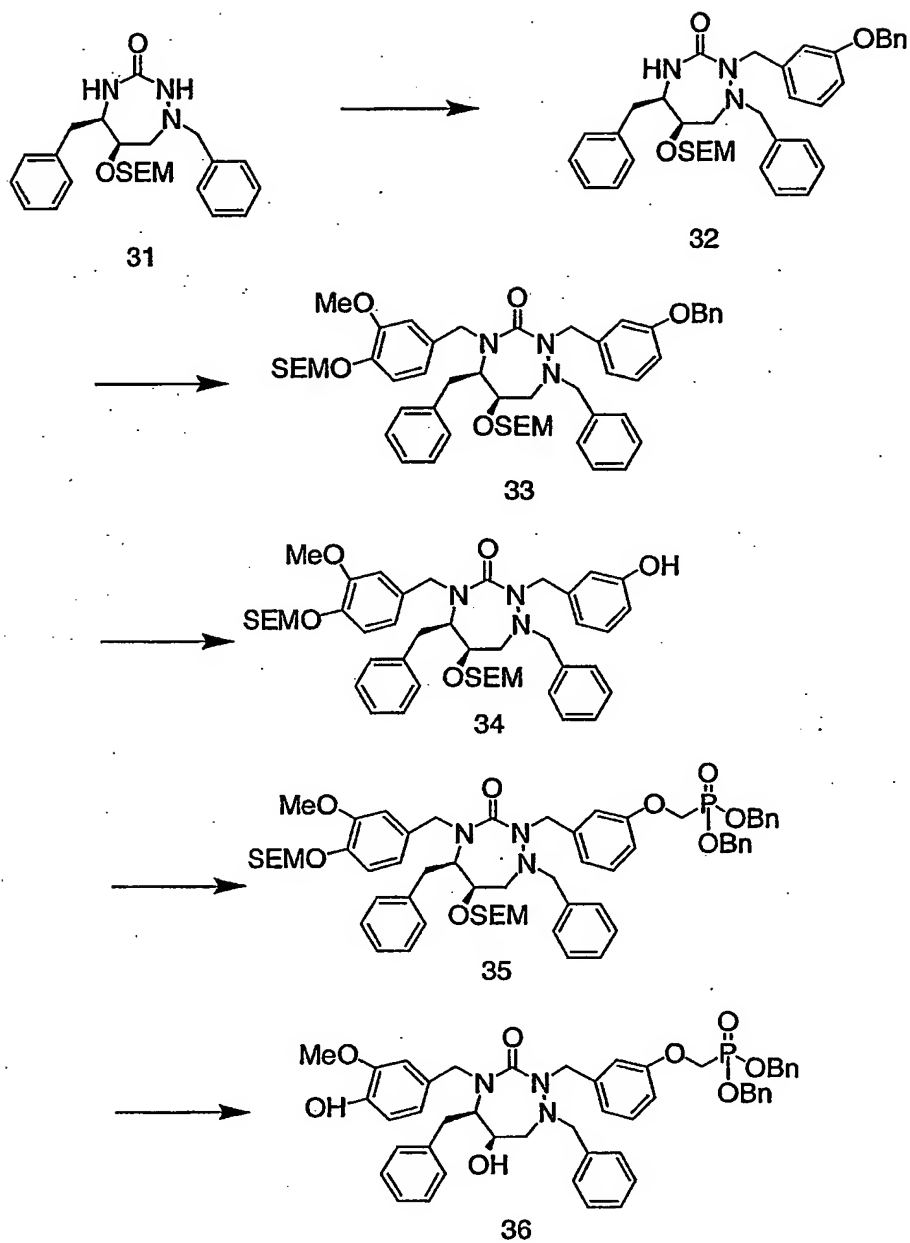
Scheme 3



## Scheme 4

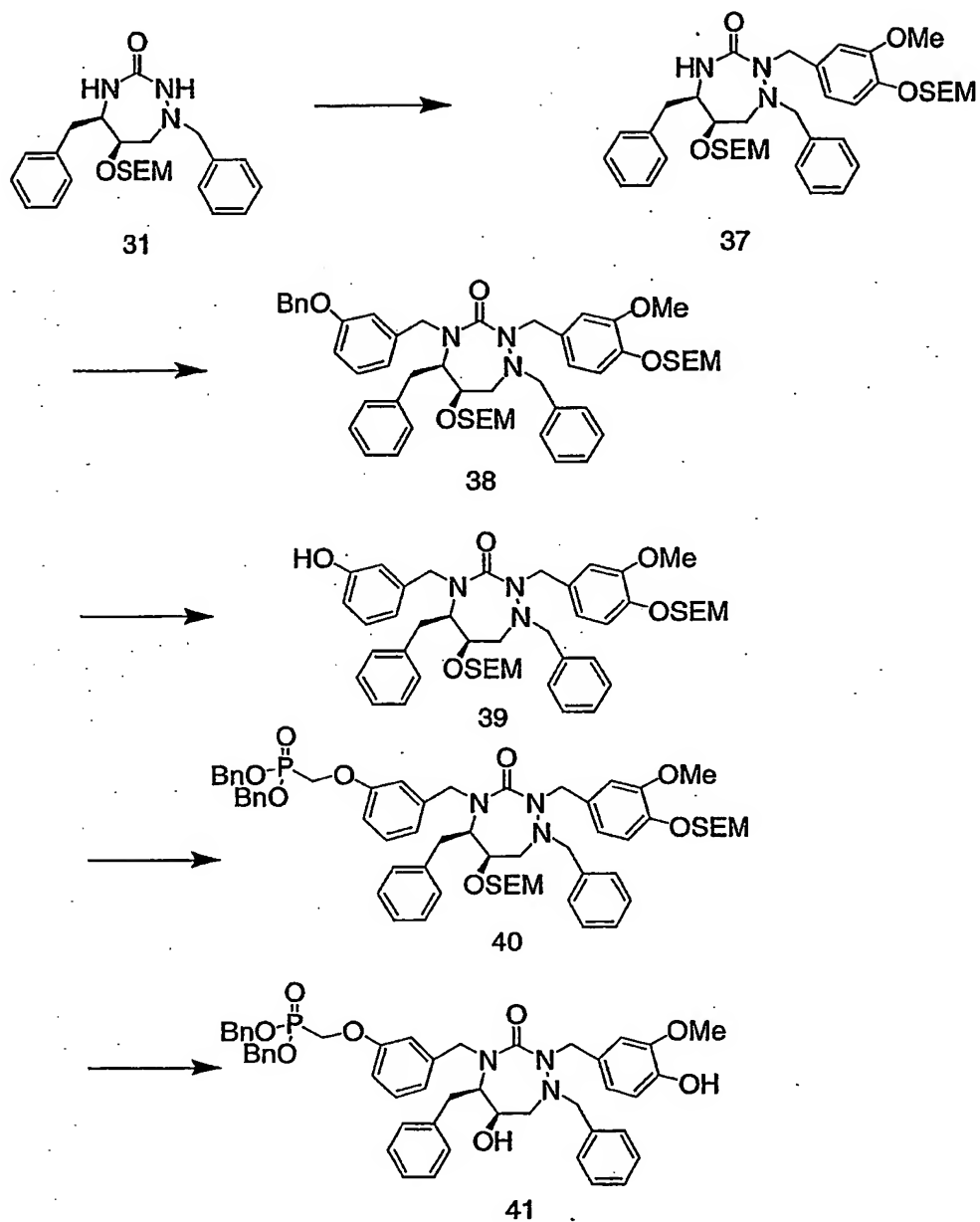


### Scheme 5





### Scheme 6



## Example Section D

### Example 1

Scheme 1 : Example; [2-(2-Benzoyloxy-phenyl)-1-oxiranyl-ethyl]-carbamic acid tert-butyl ester

5 (8)

Commercially available DL-o-tyrosine **1** (Fluka) is treated with L-aminoacid oxidase and oxygen according to the procedure of Sun et al. (J. Med. Chem. 1998, 41, 1034-1041) to afford the D-o-tyrosine **2**. Reaction with di-t-butyl-dicarbonate in the presence of base affords the boc protected amino acid **3** (J. Med. Chem. 1998, 41, 1034-1041). The boc protected acid **3** is then treated with benzyl bromide in the presence of potassium carbonate to afford the benzyl ether **4** (J. Med. Chem. 1998, 41, 1034-1041). The four step sequence reported for the preparation of the corresponding epoxide of phenylalanine (see J. Med. Chem. 1994, 37, 1758-1768) is used to prepare the desired epoxides. Thus, the acid **4** is treated with isobutylchloroformate in the presence of N-methylmorpholine to afford the mixed anhydride which is then treated with diazomethane to afford the  $\alpha$ -diazoketone **5** (see scheme 1). The ketone **5** is treated with HCl to form the  $\alpha$ -chloroketone **6** which is then reduced with sodium borohydride to form the chloro alcohol **7**. The 2S, 3R diastereoisomer is separated by chromatography and treated with base (e.g. potassium hydroxide) to afford the epoxide **8**.

20

Commercially available DL-m-tyrosine **9** (Aldrich) is resolved by treatment with  $\alpha$ -chymotrypsin to afford D-m-tyrosine **10** (Recl.: J. R. Neth. Chem. Soc. 1984, 103, 4, p110-111.) (Scheme 2). The tyrosine **10** is then treated in the same manner as the D-o-tyrosine (Scheme 1) to form the m-benzyloxy epoxide **11**.

25

The Boc-D-Tyr(Bzl)-OH acid is commercially available (Bachem) and is treated according to the four step procedure in Scheme 1 to generate the p-benzyloxy epoxide **13** shown in Scheme 3.

### 30 Example 2

Scheme 3 : Example, {4-[1-Benzyl-6-hydroxy-2,4-bis-(4-hydroxy-3-methoxy-benzyl)-3-oxo-[1,2,4]triazepan-5-ylmethyl]-phenoxy-methyl}-phosphonic acid dibenzyl ester

The boc protected benzylhydrazine 12 is prepared by condensation of boc-carbazate with benzaldehyde followed by catalytic hydrogenolysis (J. Chem. Soc. Perkin Trans. I 1975, 1712-1720). Treatment of the epoxide 13 with the boc protected benzylhydrazine 12 affords the alcohol 14 (J. Med. Chem. 1996, 39, 392-397). Benzylation of the secondary alcohol with benzylchloride in the presence of base (Green) affords the benzylether 15. Deprotection of the BOC groups with trifluoroacetic acid yields the diamine 16 (Green). CDI mediated cyclization affords the cyclic triazacycloheptanone 17 (J. Med. Chem. 1996, 39, 392-397). Alkylation of the nitrogens with [2-(4-chloromethyl-2-methoxy-phenoxy-methoxy)-ethyl]-trimethyl-silane (prepared according to the reference J. Med. Chem. 1996, 39, 392-397) affords the bis-substituted triazacycloheptanone 18 (J. Med. Chem. 1996, 39, 392-397). Catalytic hydrogenolysis affords the unprotected phenol 19 (Green) which upon alkylation with trifluoro-methanesulfonic acid bis-benzyloxy-phosphorylmethyl ester in the presence of base (e.g. cesium carbonate) yields the dibenzyl phosphonate 20. Removal of the silyl protecting groups using trimethylsilyl chloride or anhydrous HCl in methanol affords the dibenzyl phosphonate ester product 21 (J. Med. Chem. 1996, 39, 392-397).

The meta substituted analog {3-[1-Benzyl-6-hydroxy-2,4-bis-(4-hydroxy-3-methoxy-benzyl)-3-oxo-[1,2,4]triazepan-5-ylmethyl]-phenoxy-methyl}-phosphonic acid dibenzyl ester or the ortho analog, {2-[1-Benzyl-6-hydroxy-2,4-bis-(4-hydroxy-3-methoxy-benzyl)-3-oxo-[1,2,4]triazepan-5-ylmethyl]-phenoxy-methyl}-phosphonic acid dibenzyl ester, are prepared using the same methods except replacing the p-benzyloxyepoxide 13 with the meta- and ortho-substituted benzyloxy epoxides, 11 and 8, respectively.

### Example 3

Scheme 4 : Example, {4-[5-Benzyl-6-hydroxy-2,4-bis-(4-hydroxy-3-methoxy-benzyl)-3-oxo-[1,2,4]triazepan-1-ylmethyl]-phenoxy-methyl}-phosphonic acid dibenzyl ester (30)

p-Benzyloxybenzaldehyde 22 is treated with boc-carbazate and then reduced by catalytic hydrogenolysis to afford the hydrazine 23 (J. Chem. Soc. Perkin Trans. I 1975, 1712-1720).

The Boc epoxide 25 is prepared from the corresponding CBZ epoxide 24 by catalytic hydrogenolysis followed by treatment with BOC anhydride (Green). The CBZ- epoxide 24 is prepared according to the procedure of Sham et al. (J. Med. Chem. 1996, 39, 392-397).

Treatment of the epoxide 25 with the hydrazine 23 affords the alcohol 26. The alcohol 26 is treated with benzyl bromide in the presence of base (e.g. cesium carbonate) to afford the dibenzyl compound 27 (Green). The Boc groups are then removed using trifluoroacetic acid to yield diamine 28 (Green). Subjecting the diamine 28 to the same procedures shown in Scheme 1 then affords the dibenzyl phosphonate ester 29. Removal of the silyl protecting groups using trimethylsilyl chloride or anhydrous HCl in methanol affords the dibenzyl phosphonate ester product 30 (*J. Med. Chem.* 1996, 39, 392-397).

The corresponding meta- and ortho- analogs are prepared using the same procedures as in Scheme 4 except substituting p-benzyloxybenzaldehyde with m- or o-benzyloxybenzaldehyde respectively.

#### Example 4

Scheme 5: {3-[1,5-Dibenzyl-4-(4-hydroxy-3-methoxy-benzyl)-3-oxo-6-(2-trimethylsilyl-ethoxymethoxy)-[1,2,4]triazepan-2-ylmethyl]-phenoxy-methyl}-phosphonic acid dibenzyl ester (36)

The SEM protected triazacycloheptanone 31 is prepared according to the reported procedure of Sham et al. (*J. Med. Chem.* 1996, 39, 392-397). Regioselective alkylation by treatment of the triazacycloheptanone with m-benzyloxybenzylchloride and sodium hydride in DMF affords 32 which is then alkylated a second time under similar conditions to afford the bis-substituted compound 33 (*J. Med. Chem.* 1996, 39, 392-397). Catalytic hydrogenolysis affords the phenol 34 (Green). Alkylation with trifluoro-methanesulfonic acid bis-benzyloxy-phosphorylmethyl ester using the standard conditions affords the dibenzyl ester 35. Removal of the silyl protecting groups using trimethylsilyl chloride or anhydrous HCl in methanol affords the dibenzyl phosphonate ester product 36 (*J. Med. Chem.* 1996, 39, 392-397).

Ortho analog {2-[1,5-Dibenzyl-4-(4-hydroxy-3-methoxy-benzyl)-3-oxo-6-(2-trimethylsilyl-ethoxymethoxy)-[1,2,4]triazepan-2-ylmethyl]-phenoxy-methyl}-phosphonic acid dibenzyl ester and para analog {4-[1,5-Dibenzyl-4-(4-hydroxy-3-methoxy-benzyl)-3-oxo-6-(2-trimethylsilyl-ethoxymethoxy)-[1,2,4]triazepan-2-ylmethyl]-phenoxy-methyl}-phosphonic acid dibenzyl ester are prepared using the same procedures except substituting o-benzyloxybenzylchloride and p-benzyloxybenzylchloride respectively, for the m-benzyloxybenzylchloride. O-benzyloxybenzylchloride is prepared from o-

benzyloxybenzaldehyde by reduction with sodium borohydride and then treatment with methanesulfonylchloride (J. Med. Chem. 1996, 39, 392-397).

#### Example 5

- 5 Scheme 6: {3-[1,5-Dibenzyl-6-hydroxy-2-(4-hydroxy-3-methoxy-benzyl)-3-oxo-[1,2,4]triazepan-4-ylmethyl]-phenoxy-methyl}-phosphonic acid dibenzyl ester (41)

The SEM protected triazacycloheptanone 31 is prepared according to the reported procedure of Sham et al. (J. Med. Chem. 1996, 39, 392-397). Regioselective alkylation by treatment of the triazacycloheptanone with SEM protected benzylchloride and sodium hydride  
10 in DMF affords 37 which is then alkylated with m-benzyloxybenzylchloride under similar conditions to afford the bis-substituted compound 38 (J. Med. Chem. 1996, 39, 392-397). Catalytic hydrogenolysis affords the phenol 39 (Green). Alkylation with trifluoromethanesulfonic acid bis-benzyloxy-phosphorylmethyl ester using the standard conditions affords the dibenzyl ester 40. Removal of the silyl protecting groups using trimethylsilyl  
15 chloride or anhydrous HCl in methanol affords the dibenzyl phosphonate ester product 41 (J. Med. Chem. 1996, 39, 392-397).

Ortho analog, {2-[1,5-Dibenzyl-6-hydroxy-2-(4-hydroxy-3-methoxy-benzyl)-3-oxo-[1,2,4]triazepan-4-ylmethyl]-phenoxy-methyl}-phosphonic acid dibenzyl ester and para analog,  
20 {4-[1,5-Dibenzyl-6-hydroxy-2-(4-hydroxy-3-methoxy-benzyl)-3-oxo-[1,2,4]triazepan-4-ylmethyl]-phenoxy-methyl}-phosphonic acid dibenzyl ester are prepared using the same procedures except substituting o-benzyloxybenzylchloride and p-benzyloxybenzylchloride respectively, for the m-benzyloxybenzylchloride.

### Scheme General Section

General aspects of these exemplary methods are described below and in the Example. Each of the products of the following processes is optionally separated, isolated, and/or purified prior to its use in subsequent processes.

5 The terms "treated", "treating", "treatment", and the like, mean contacting, mixing, reacting, allowing to react, bringing into contact, and other terms common in the art for indicating that one or more chemical entities is treated in such a manner as to convert it to one or more other chemical entities. This means that "treating compound one with compound two" is synonymous with "allowing compound one to react with compound two", "contacting  
10 compound one with compound two", "reacting compound one with compound two", and other expressions common in the art of organic synthesis for reasonably indicating that compound one was "treated", "reacted", "allowed to react", etc., with compound two.

"Treating" indicates the reasonable and usual manner in which organic chemicals are allowed to react. Normal concentrations (0.01M to 10M, typically 0.1M to 1M),  
15 temperatures (-100°C to 250°C, typically -78°C to 150°C, more typically -78°C to 100°C, still more typically 0°C to 100°C), reaction vessels (typically glass, plastic, metal), solvents, pressures, atmospheres (typically air for oxygen and water insensitive reactions or nitrogen or argon for oxygen or water sensitive), etc., are intended unless otherwise indicated. The knowledge of similar reactions known in the art of organic synthesis is used in selecting the  
20 conditions and apparatus for "treating" in a given process. In particular, one of ordinary skill in the art of organic synthesis selects conditions and apparatus reasonably expected to successfully carry out the chemical reactions of the described processes based on the knowledge in the art.

Modifications of each of the exemplary schemes above and in the examples (hereafter  
25 "exemplary schemes") leads to various analogs of the specific exemplary materials produce. The above cited citations describing suitable methods of organic synthesis are applicable to such modifications.

In each of the exemplary schemes it may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step  
30 or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example, size exclusion or ion exchange chromatography, high, medium, or  
35 low pressure liquid chromatography, small scale and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography.

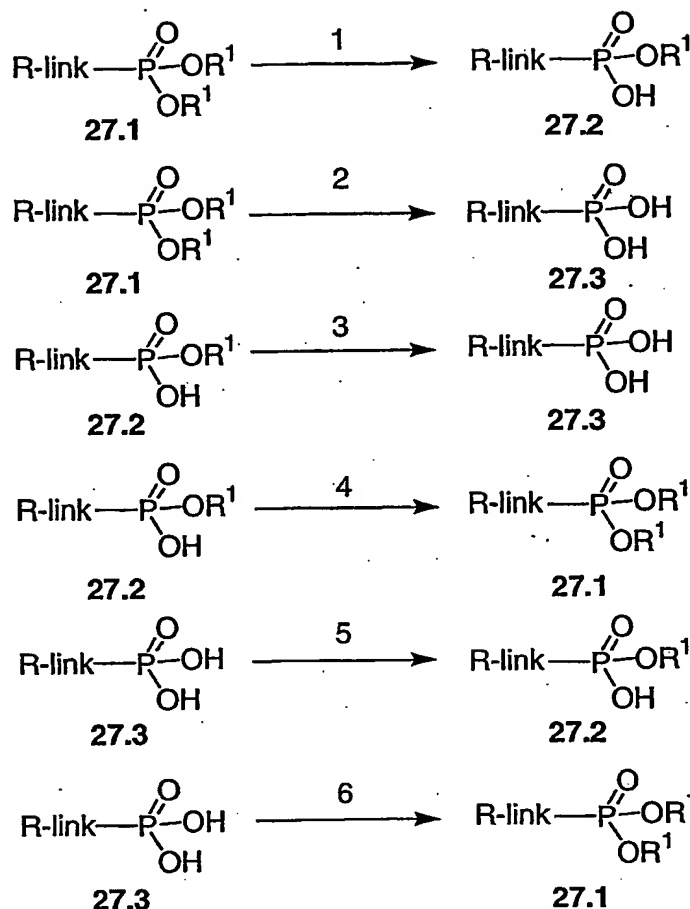
Another class of separation methods involves treatment of a mixture with a reagent

selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents or absorbents such as activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like.

Selection of appropriate methods of separation depends on the nature of the materials involved. For example, boiling point, and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like. One skilled in the art will apply techniques most likely to achieve the desired separation.

All literature and patent citations above are hereby expressly incorporated by reference at the locations of their citation. Specifically cited sections or pages of the above cited works are incorporated by reference with specificity. The invention has been described in detail sufficient to allow one of ordinary skill in the art to make and use the subject matter of the following Embodiments. It is apparent that certain modifications of the methods and compositions of the following Embodiments can be made within the scope and spirit of the invention.

Scheme 1001



Scheme 1001 shows the interconversions of certain phosphonate compounds: acids -  
 5  $\text{P}(\text{O})(\text{OH})_2$ ; mono-esters  $-\text{P}(\text{O})(\text{OR}^1)(\text{OH})$ ; and diesters  $-\text{P}(\text{O})(\text{OR}^1)_2$  in which the  $\text{R}^1$  groups  
 are independently selected, and defined herein before, and the phosphorus is attached through  
 a carbon moiety (link, i.e. linker), which is attached to the rest of the molecule, e.g. drug or  
 drug intermediate (R). The  $\text{R}^1$  groups attached to the phosphonate esters in Scheme 1001  
 may be changed using established chemical transformations. The interconversions may be  
 10 carried out in the precursor compounds or the final products using the methods described  
 below. The methods employed for a given phosphonate transformation depend on the nature  
 of the substituent  $\text{R}^1$ . The preparation and hydrolysis of phosphonate esters is described in  
Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester 27.1 into the corresponding phosphonate  
 15 monoester 27.2 (Scheme 1001, Reaction 1) can be accomplished by a number of methods.



For example, the ester 27.1 in which R<sup>1</sup> is an arylalkyl group such as benzyl, can be converted into the monoester compound 27.2 by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in *J. Org. Chem.*, 1995, 60:2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°C. The conversion of the diester 27.1 in which R<sup>1</sup> is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester 27.2 can be effected by treatment of the ester 27.1 with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters 27.2 in which one of the groups R<sup>1</sup> is arylalkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters 27.2 in which R<sup>1</sup> is alkyl, by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R<sup>1</sup> are alkenyl, such as allyl, can be converted into the monoester 27.2 in which R<sup>1</sup> is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in *J. Org. Chem.*, 38:3224 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester 27.1 or a phosphonate monoester 27.2 into the corresponding phosphonic acid 27.3 (Scheme 1001, Reactions 2 and 3) can be effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in *J. Chem. Soc., Chem. Comm.*, 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester 27.2 in which R<sup>1</sup> is arylalkyl such as benzyl, can be converted into the corresponding phosphonic acid 27.3 by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxane. A phosphonate monoester 27.2 in which R<sup>1</sup> is alkenyl such as, for example, allyl, can be converted into the phosphonic acid 27.3 by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in *Helv. Chim. Acta.*, 68:618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters 27.1 in which R<sup>1</sup> is benzyl is described in *J. Org. Chem.*, 24:434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters 27.1 in which R<sup>1</sup> is phenyl is described in *J. Amer. Chem. Soc.*, 78:2336, 1956.

The conversion of a phosphonate monoester 27.2 into a phosphonate diester 27.1 (Scheme 1001, Reaction 4) in which the newly introduced R<sup>1</sup> group is alkyl, arylalkyl, or

haloalkyl such as chloroethyl, can be effected by a number of reactions in which the substrate 27.2 is reacted with a hydroxy compound  $R^1OH$ , in the presence of a coupling agent.

Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is

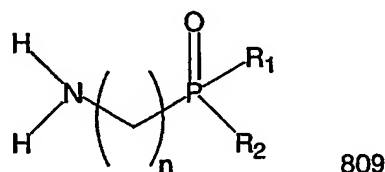
- 5 preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl
- 10 phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester 27.1 to the diester 27.1 can be effected by the use of the Mitsunobu reaction. The substrate is reacted with the hydroxy compound  $R^1OH$ , in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester 27.2 can be transformed into the phosphonate diester 27.1, in which
- 15 the introduced  $R^1$  group is alkenyl or arylalkyl, by reaction of the monoester with the halide  $R^1Br$ , in which  $R^1$  is as alkenyl or arylalkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester
- 20 27.2 is transformed into the chloro analog  $-P(O)(OR^1)Cl$  by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product  $-P(O)(OR^1)Cl$  is then reacted with the hydroxy compound  $R^1OH$ , in the presence of a base such as triethylamine, to afford the phosphonate diester 27.1.

- 25 A phosphonic acid  $-P(O)(OH)_2$  can be transformed into a phosphonate monoester  $-P(O)(OR^1)(OH)$  (Scheme 1001, Reaction 5) by means of the methods described above of for the preparation of the phosphonate diester  $-P(O)(OR^1)_2$  27.1, except that only one molar proportion of the component  $R^1OH$  or  $R^1Br$  is employed.

- A phosphonic acid  $-P(O)(OH)_2$  27.3 can be transformed into a phosphonate diester
- 30  $-P(O)(OR^1)_2$  27.1 (Scheme 1, Reaction 6) by a coupling reaction with the hydroxy compound  $R^1OH$ , in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids 27.3 can be transformed into phosphonic esters 27.1 in which

R<sup>1</sup> is aryl, such as phenyl, by means of a coupling reaction employing, for example, phenol and dicyclohexylcarbodiimide in pyridine at about 70°C. Alternatively, phosphonic acids 27.3 can be transformed into phosphonic esters 27.1 in which R<sup>1</sup> is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R<sup>1</sup>Br in a polar organic solvent such as acetonitrile solution at reflux temperature, in the presence of a base such as cesium carbonate, to afford the phosphonic ester 27.1.

Amino alkyl phosphonate compounds 809:



10

are a generic representative of compounds 811, 813, 814, 816 and 818. Some methods to prepare embodiments of 809 are shown in Scheme 1002. Commercial amino phosphonic acid 810 was protected as carbamate 811. The phosphonic acid 811 was converted to phosphonate 812 upon treatment with ROH in the presence of DCC or other conventional coupling reagents. Coupling of phosphonic acid 811 with esters of amino acid 820 provided bisamidate 817. Conversion of acid 811 to bisphenyl phosphonate followed by hydrolysis gave mono-phosphonic acid 814 (Cbz = C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>C(O)-), which was then transformed to mono-phosphonic amidate 815. Carbamates 813, 816 and 818 were converted to their corresponding amines upon hydrogenation. Compounds 811, 813, 814, 816 and 818 are useful intermediates to form the phosphonate compounds of the invention.

20

**Preparation of carboalkoxy-substituted phosphonate bisamidates, monoamidates, diesters and monoesters.**

25 A number of methods are available for the conversion of phosphonic acids into amidates and esters. In one group of methods, the phosphonic acid is either converted into an isolated activated intermediate such as a phosphoryl chloride, or the phosphonic acid is activated in situ for reaction with an amine or a hydroxy compound.

- The conversion of phosphonic acids into phosphoryl chlorides is accomplished by reaction with thionyl chloride, for example as described in J. Gen. Chem. USSR, 1983, 53, 480, Zh. Obschei Khim., 1958, 28, 1063, or J. Org. Chem., 1994, 59, 6144, or by reaction with oxalyl chloride, as described in J. Am. Chem. Soc., 1994, 116, 3251, or J. Org. Chem., 1994, 59, 6144, or by reaction with phosphorus pentachloride, as described in J. Org. Chem., 2001, 66, 329, or in J. Med. Chem., 1995, 38, 1372. The resultant phosphoryl chlorides are then reacted with amines or hydroxy compounds in the presence of a base to afford the amidate or ester products.
- 10 Phosphonic acids are converted into activated imidazolyl derivatives by reaction with carbonyl diimidazole, as described in J. Chem. Soc., Chem. Comm., 1991, 312, or Nucleosides Nucleotides 2000, 19, 1885. Activated sulfonyloxy derivatives are obtained by the reaction of phosphonic acids with trichloromethylsulfonyl chloride, as described in J. Med. Chem. 1995, 38, 4958, or with triisopropylbenzenesulfonyl chloride, as described in
- 15 Tet. Lett., 1996, 7857, or Bioorg. Med. Chem. Lett., 1998, 8, 663. The activated sulfonyloxy derivatives are then reacted with amines or hydroxy compounds to afford amidates or esters. Alternatively, the phosphonic acid and the amine or hydroxy reactant are combined in the presence of a diimide coupling agent. The preparation of phosphonic amidates and esters by means of coupling reactions in the presence of dicyclohexyl carbodiimide is described, for example, in J. Chem. Soc., Chem. Comm., 1991, 312, or J. Med. Chem., 1980, 23, 1299 or
- 20 Coll. Czech. Chem. Comm., 1987, 52, 2792. The use of ethyl dimethylaminopropyl carbodiimide for activation and coupling of phosphonic acids is described in Tet. Lett., 2001, 42, 8841, or Nucleosides Nucleotides, 2000, 19, 1885.
- 25 A number of additional coupling reagents have been described for the preparation of amidates and esters from phosphonic acids. The agents include Aldrithiol-2, and PYBOP and BOP, as described in J. Org. Chem., 1995, 60, 5214, and J. Med. Chem., 1997, 40, 3842, mesitylene-2-sulfonyl-3-nitro-1,2,4-triazole (MSNT), as described in J. Med. Chem., 1996, 39, 4958, diphenylphosphoryl azide, as described in J. Org. Chem., 1984, 49, 1158, 1-(2,4,6-
- 30 triisopropylbenzenesulfonyl-3-nitro-1,2,4-triazole (TPSNT) as described in Bioorg. Med. Chem. Lett., 1998, 8, 1013, bromotris(dimethylamino)phosphonium hexafluorophosphate (BroP), as described in Tet. Lett., 1996, 37, 3997, 2-chloro-5,5-dimethyl-2-oxo-1,3,2-

dioxaphosphinane, as described in Nucleosides Nucleotides 1995, 14, 871, and diphenyl chlorophosphate, as described in J. Med. Chem., 1988, 31, 1305.

Phosphonic acids are converted into amidates and esters by means of the Mitsunobu reaction, in which the phosphonic acid and the amine or hydroxy reactant are combined in the presence of a triaryl phosphine and a dialkyl azodicarboxylate. The procedure is described in Org. Lett., 2001, 3, 643, or J. Med. Chem., 1997, 40, 3842.

Phosphonic esters are also obtained by the reaction between phosphonic acids and halo compounds, in the presence of a suitable base. The method is described, for example, in Anal. Chem., 1987, 59, 1056, or J. Chem. Soc. Perkin Trans., I, 1993, 19, 2303, or J. Med. Chem., 1995, 38, 1372, or Tet. Lett., 2002, 43, 1161.

Schemes 1 - 4 illustrate the conversion of phosphonate esters and phosphonic acids into carboalkoxy-substituted phosphorobisamidates (Scheme 1), phosphoroamidates (Scheme 2), phosphonate monoesters (Scheme 3) and phosphonate diesters, (Scheme 4).

Scheme 1 illustrates various methods for the conversion of phosphonate diesters 1.1 into phosphorobisamidates 1.5. The diester 1.1, prepared as described previously, is hydrolyzed, either to the monoester 1.2 or to the phosphonic acid 1.6. The methods employed for these transformations are described above. The monoester 1.2 is converted into the monoamidate 1.3 by reaction with an aminoester 1.9, in which the group  $R^2$  is H or alkyl, the group  $R^4$  is an alkylene moiety such as, for example,  $\text{CHCH}_3$ ,  $\text{CHPr}^1$ ,  $\text{CH}(\text{CH}_2\text{Ph})$ ,  $\text{CH}_2\text{CH}(\text{CH}_3)$  and the like, or a group present in natural or modified aminoacids, and the group  $R^5$  is alkyl. The reactants are combined in the presence of a coupling agent such as a carbodiimide, for example dicyclohexyl carbodiimide, as described in J. Am. Chem. Soc., 1957, 79, 3575, optionally in the presence of an activating agent such as hydroxybenztriazole, to yield the amidate product 1.3. The amidate-forming reaction is also effected in the presence of coupling agents such as BOP, as described in J. Org. Chem., 1995, 60, 5214, Aldrithiol, PYBOP and similar coupling agents used for the preparation of amides and esters. Alternatively, the reactants 1.2 and 1.9 are transformed into the monoamidate 1.3 by means of a Mitsunobu reaction. The preparation of amidates by means of the Mitsunobu reaction is described in J. Med. Chem., 1995, 38, 2742. Equimolar amounts of the reactants are

combined in an inert solvent such as tetrahydrofuran in the presence of a triaryl phosphine and a dialkyl azodicarboxylate. The thus-obtained monoamidate ester 1.3 is then transformed into amidate phosphonic acid 1.4. The conditions used for the hydrolysis reaction depend on the nature of the R<sup>1</sup> group, as described previously. The phosphonic acid amidate 1.4 is then  
5 reacted with an aminoester 1.9, as described above, to yield the bisamidate product 1.5, in which the amino substituents are the same or different.

An example of this procedure is shown in Scheme 1, Example 1. In this procedure, a dibenzyl phosphonate 1.14 is reacted with diazabicyclooctane (DABCO) in toluene at reflux,  
10 as described in J. Org. Chem., 1995, 60, 2946, to afford the monobenzyl phosphonate 1.15. The product is then reacted with equimolar amounts of ethyl alaninate 1.16 and dicyclohexyl carbodiimide in pyridine, to yield the amidate product 1.17. The benzyl group is then removed, for example by hydrogenolysis over a palladium catalyst, to give the monoacid product 1.18. This compound is then reacted in a Mitsunobu reaction with ethyl leucinate  
15 1.19, triphenyl phosphine and diethylazodicarboxylate, as described in J. Med. Chem., 1995, 38, 2742, to produce the bisamidate product 1.20.

Using the above procedures, but employing, in place of ethyl leucinate 1.19 or ethyl alaninate 1.16, different aminoesters 1.9, the corresponding products 1.5 are obtained.

20 Alternatively, the phosphonic acid 1.6 is converted into the bisamidate 1.5 by use of the coupling reactions described above. The reaction is performed in one step, in which case the nitrogen-related substituents present in the product 1.5 are the same, or in two steps, in which case the nitrogen-related substituents can be different.

25 An example of the method is shown in Scheme 1, Example 2. In this procedure, a phosphonic acid 1.6 is reacted in pyridine solution with excess ethyl phenylalaninate 1.21 and dicyclohexylcarbodiimide, for example as described in J. Chem. Soc., Chem. Comm., 1991, 1063, to give the bisamidate product 1.22.

30 Using the above procedures, but employing, in place of ethyl phenylalaninate, different aminoesters 1.9, the corresponding products 1.5 are obtained.

As a further alternative, the phosphonic acid **1.6** is converted into the mono or bis-activated derivative **1.7**, in which Lv is a leaving group such as chloro, imidazolyl, triisopropylbenzenesulfonyloxy etc. The conversion of phosphonic acids into chlorides **1.7** (Lv = Cl) is effected by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17. The conversion of phosphonic acids into monoimidazolides **1.7** (Lv = imidazolyl) is described in J. Med. Chem., 2002, 45, 1284 and in J. Chem. Soc. Chem. Comm., 1991, 312. Alternatively, the phosphonic acid is activated by reaction with triisopropylbenzenesulfonyl chloride, as described in Nucleosides and Nucleotides, 2000, 10, 1885. The activated product is then reacted with the aminoester **1.9**, in the presence of a base, to give the bisamidate **1.5**. The reaction is performed in one step, in which case the nitrogen substituents present in the product **1.5** are the same, or in two steps, via the intermediate **1.11**, in which case the nitrogen substituents can be different.

Examples of these methods are shown in Scheme 1, Examples 3 and 5. In the procedure illustrated in Scheme 1, Example 3, a phosphonic acid **1.6** is reacted with ten molar equivalents of thionyl chloride, as described in Zh. Obschei Khim., 1958, 28, 1063, to give the dichloro compound **1.23**. The product is then reacted at reflux temperature in a polar aprotic solvent such as acetonitrile, and in the presence of a base such as triethylamine, with butyl serinate **1.24** to afford the bisamidate product **1.25**.

Using the above procedures, but employing, in place of butyl serinate **1.24**, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

In the procedure illustrated in Scheme 1, Example 5, the phosphonic acid **1.6** is reacted, as described in J. Chem. Soc. Chem. Comm., 1991, 312, with carbonyl diimidazole to give the imidazolide **1.32**. The product is then reacted in acetonitrile solution at ambient temperature, with one molar equivalent of ethyl alaninate **1.33** to yield the monodisplacement product **1.34**. The latter compound is then reacted with carbonyl diimidazole to produce the activated intermediate **1.35**, and the product is then reacted, under the same conditions, with ethyl N-methylalaninate **1.33a** to give the bisamidate product **1.36**.

Using the above procedures, but employing, in place of ethyl alaninate 1.33 or ethyl N-methylalaninate 1.33a, different aminoesters 1.9, the corresponding products 1.5 are obtained.

- 5 The intermediate monoamidate 1.3 is also prepared from the monoester 1.2 by first converting the monoester into the activated derivative 1.8 in which Lv is a leaving group such as halo, imidazolyl etc, using the procedures described above. The product 1.8 is then reacted with an aminoester 1.9 in the presence of a base such as pyridine, to give an intermediate monoamidate product 1.3. The latter compound is then converted, by removal  
10 of the R<sup>1</sup> group and coupling of the product with the aminoester 1.9, as described above, into the bisamidate 1.5.

- An example of this procedure, in which the phosphonic acid is activated by conversion to the chloro derivative 1.26, is shown in Scheme 1, Example 4. In this procedure, the phosphonic  
15 monobenzyl ester 1.15 is reacted, in dichloromethane, with thionyl chloride, as described in Tet. Let., 1994, 35, 4097, to afford the phosphoryl chloride 1.26. The product is then reacted in acetonitrile solution at ambient temperature with one molar equivalent of ethyl 3-amino-2-methylpropionate 1.27 to yield the monoamidate product 1.28. The latter compound is hydrogenated in ethyl acetate over a 5% palladium on carbon catalyst to produce the  
20 monoacid product 1.29. The product is subjected to a Mitsunobu coupling procedure, with equimolar amounts of butyl alaninate 1.30, triphenyl phosphine, diethylazodicarboxylate and triethylamine in tetrahydrofuran, to give the bisamidate product 1.31.

- Using the above procedures, but employing, in place of ethyl 3-amino-2-methylpropionate  
25 1.27 or butyl alaninate 1.30, different aminoesters 1.9, the corresponding products 1.5 are obtained.

- The activated phosphonic acid derivative 1.7 is also converted into the bisamidate 1.5 via the diamino compound 1.10. The conversion of activated phosphonic acid derivatives such as  
30 phosphoryl chlorides into the corresponding amino analogs 1.10, by reaction with ammonia, is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976. The diamino compound 1.10 is then reacted at elevated temperature with a haloester



1.12, in a polar organic solvent such as dimethylformamide, in the presence of a base such as dimethylaminopyridine or potassium carbonate, to yield the bisamidate 1.5.

An example of this procedure is shown in Scheme 1, Example 6. In this method, a dichlorophosphonate 1.23 is reacted with ammonia to afford the diamide 1.37. The reaction is performed in aqueous, aqueous alcoholic or alcoholic solution, at reflux temperature. The resulting diamino compound is then reacted with two molar equivalents of ethyl 2-bromo-3-methylbutyrate 1.38, in a polar organic solvent such as N-methylpyrrolidinone at ca. 150°C, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, to afford the bisamidate product 1.39.

Using the above procedures, but employing, in place of ethyl 2-bromo-3-methylbutyrate 1.38, different haloesters 1.12 the corresponding products 1.5 are obtained.

The procedures shown in Scheme 1 are also applicable to the preparation of bisamidates in which the aminoester moiety incorporates different functional groups. Scheme 1, Example 7 illustrates the preparation of bisamidates derived from tyrosine. In this procedure, the monoimidazolidine 1.32 is reacted with propyl tyrosinate 1.40, as described in Example 5, to yield the monoamidate 1.41. The product is reacted with carbonyl diimidazole to give the imidazolidine 1.42, and this material is reacted with a further molar equivalent of propyl tyrosinate to produce the bisamidate product 1.43.

Using the above procedures, but employing, in place of propyl tyrosinate 1.40, different aminoesters 1.9, the corresponding products 1.5 are obtained. The aminoesters employed in the two stages of the above procedure can be the same or different, so that bisamidates with the same or different amino substituents are prepared.

Scheme 2 illustrates methods for the preparation of phosphonate monoamidates.

In one procedure, a phosphonate monoester 1.1 is converted, as described in Scheme 1, into the activated derivative 1.8. This compound is then reacted, as described above, with an aminoester 1.9, in the presence of a base, to afford the monoamidate product 2.1.

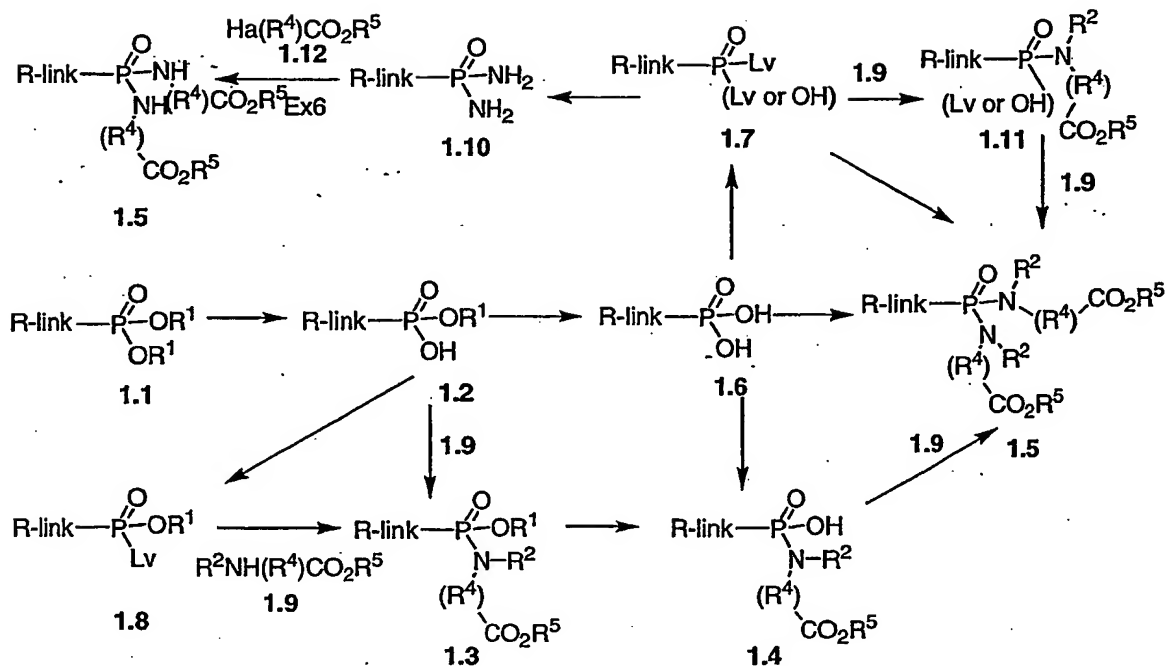
The procedure is illustrated in Scheme 2, Example 1. In this method, a monophenyl phosphonate 2.7 is reacted with, for example, thionyl chloride, as described in J. Gen. Chem.

USSR., 1983, 32, 367, to give the chloro product 2.8. The product is then reacted, as described in Scheme 1, with ethyl alaninate 2.9, to yield the amidate 2.10.

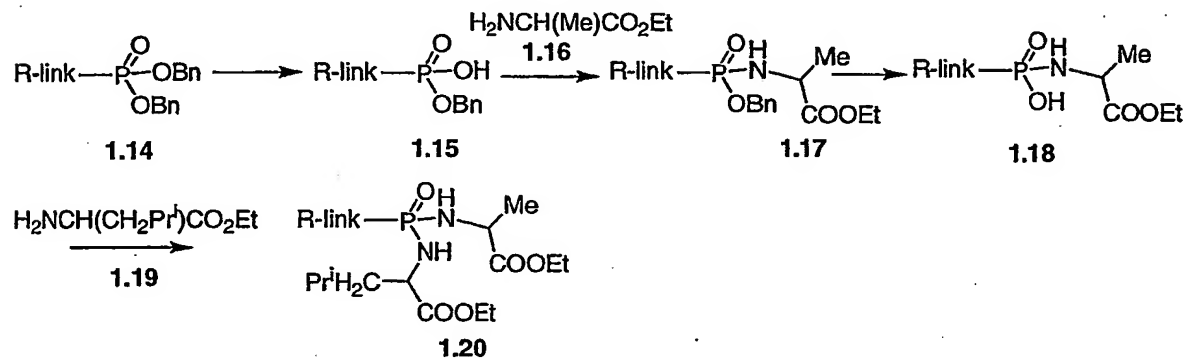
5 Using the above procedures, but employing, in place of ethyl alaninate 2.9, different aminoesters 1.9, the corresponding products 2.1 are obtained.

10 Alternatively, the phosphonate monoester 1.1 is coupled, as described in Scheme 1, with an aminoester 1.9 to produce the amidate 2.1. If necessary, the R<sup>1</sup> substituent is then altered, by initial cleavage to afford the phosphonic acid 2.2. The procedures for this transformation depend on the nature of the R<sup>1</sup> group, and are described above. The phosphonic acid is then transformed into the ester amidate product 2.3, by reaction with the hydroxy compound R<sup>3</sup>OH, in which the group R<sup>3</sup> is aryl, heteroaryl, alkyl, cycloalkyl, haloalkyl etc, using the same coupling procedures (carbodiimide, Aldrichol-2, PYBOP, Mitsunobu reaction etc) described in Scheme 1 for the coupling of amines and phosphonic acids.

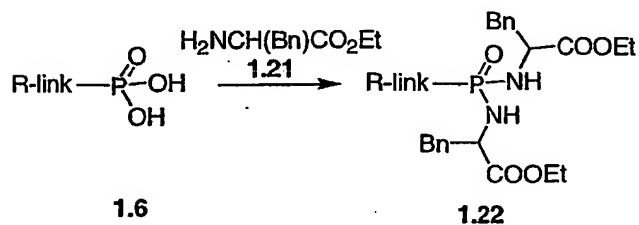
## Scheme 1



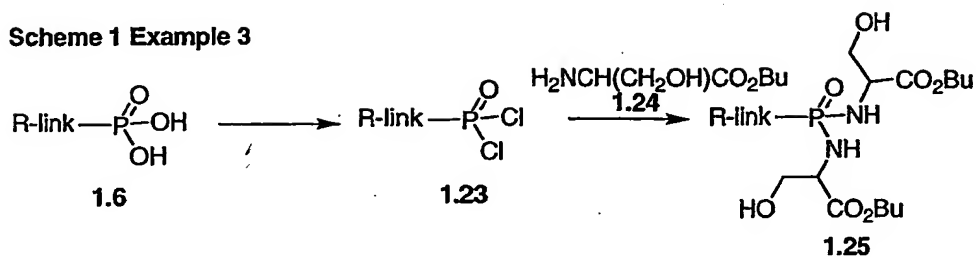
## Scheme 1 Example 1



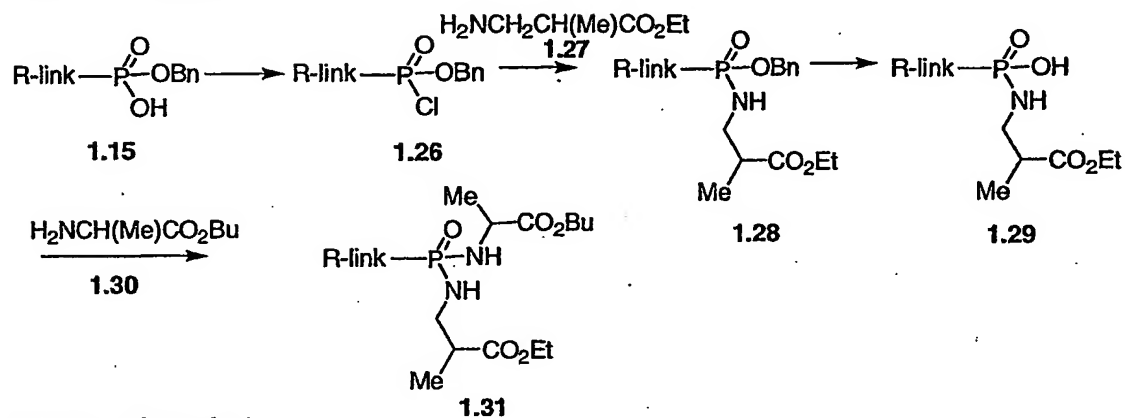
## Scheme 1 Example 2



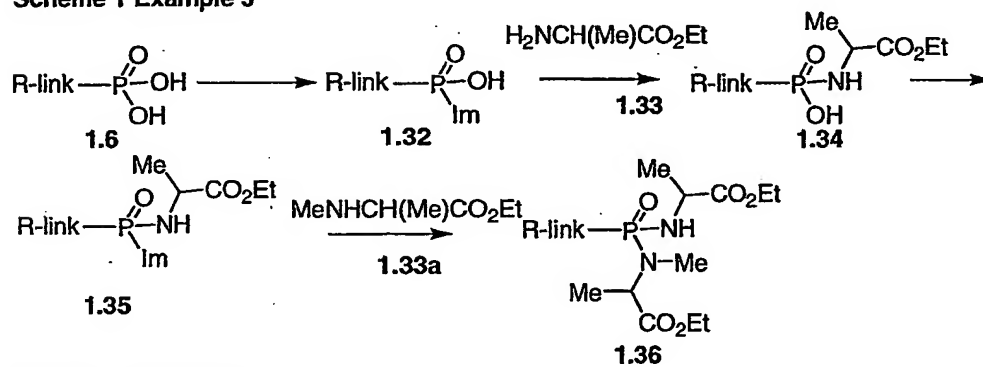
## Scheme 1 Example 3



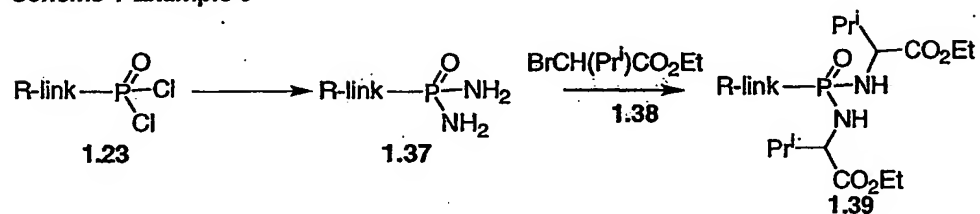
## Scheme 1 Example 4



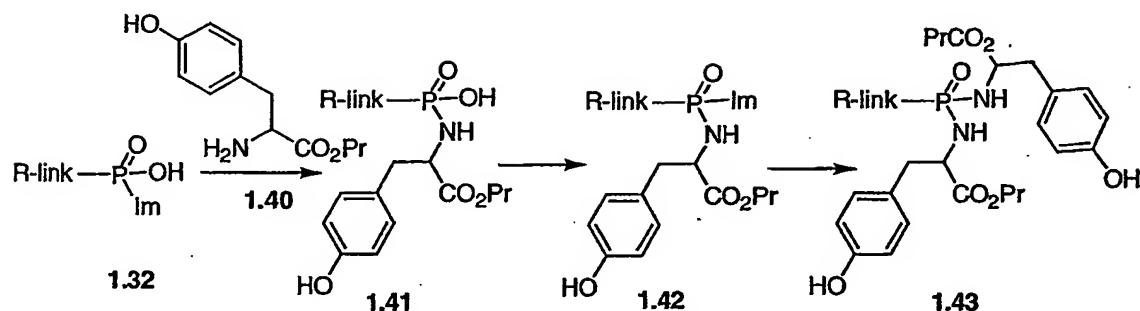
## Scheme 1 Example 5



## Scheme 1 Example 6



## Scheme 1 Example 7



Examples of this method are shown in Scheme 2, Examples and 2 and 3. In the sequence shown in Example 2, a monobenzyl phosphonate **2.11** is transformed by reaction with ethyl alaninate, using one of the methods described above, into the monoamidate **2.12**. The benzyl group is then removed by catalytic hydrogenation in ethyl acetate solution over a 5% palladium on carbon catalyst, to afford the phosphonic acid amidate **2.13**. The product is then reacted in dichloromethane solution at ambient temperature with equimolar amounts of 1-(dimethylaminopropyl)-3-ethylcarbodiimide and trifluoroethanol **2.14**, for example as described in Tet. Lett., 2001, 42, 8841, to yield the amidate ester **2.15**.

In the sequence shown in Scheme 2, Example 3, the monoamidate **2.13** is coupled, in tetrahydrofuran solution at ambient temperature, with equimolar amounts of dicyclohexyl carbodiimide and 4-hydroxy-N-methylpiperidine **2.16**, to produce the amidate ester product **2.17**.

Using the above procedures, but employing, in place of the ethyl alaninate product **2.12** different monoacids **2.2**, and in place of trifluoroethanol **2.14** or 4-hydroxy-N-methylpiperidine **2.16**, different hydroxy compounds  $\text{R}^3\text{OH}$ , the corresponding products **2.3** are obtained.

Alternatively, the activated phosphonate ester **1.8** is reacted with ammonia to yield the amidate **2.4**. The product is then reacted, as described in Scheme 1, with a haloester **2.5**, in the presence of a base, to produce the amidate product **2.6**. If appropriate, the nature of the  $\text{R}^1$  group is changed, using the procedures described above, to give the product **2.3**. The method is illustrated in Scheme 2, Example 4. In this sequence, the monophenyl phosphoryl

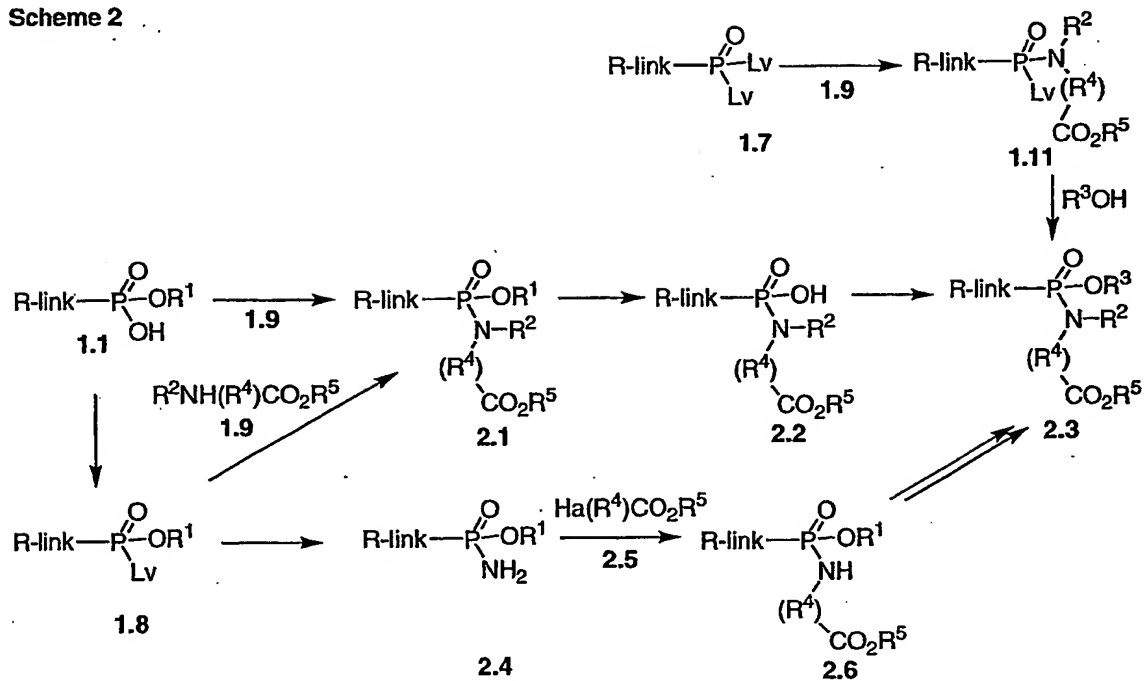
chloride **2.18** is reacted, as described in Scheme 1, with ammonia, to yield the amino product **2.19**. This material is then reacted in N-methylpyrrolidinone solution at 170°C with butyl 2-bromo-3-phenylpropionate **2.20** and potassium carbonate, to afford the amidate product **2.21**. Using these procedures, but employing, in place of butyl 2-bromo-3-phenylpropionate **2.20**,  
5 different haloesters **2.5**, the corresponding products **2.6** are obtained.

The monoamidate products **2.3** are also prepared from the doubly activated phosphonate derivatives **1.7**. In this procedure, examples of which are described in Synlett., 1998, 1, 73, the intermediate **1.7** is reacted with a limited amount of the aminoester **1.9** to give the mono-  
10 displacement product **1.11**. The latter compound is then reacted with the hydroxy compound  $R^3OH$  in a polar organic solvent such as dimethylformamide, in the presence of a base such as diisopropylethylamine, to yield the monoamidate ester **2.3**.

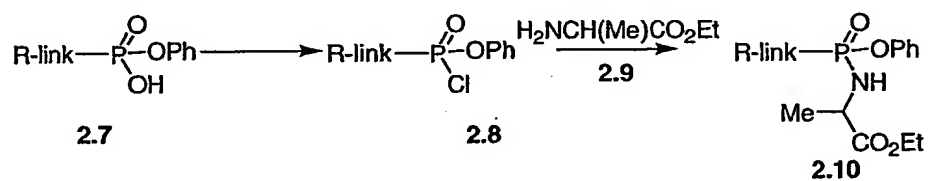
The method is illustrated in Scheme 2, Example 5. In this method, the phosphoryl dichloride  
15 **2.22** is reacted in dichloromethane solution with one molar equivalent of ethyl N-methyl tyrosinate **2.23** and dimethylaminopyridine, to generate the monoamidate **2.24**. The product is then reacted with phenol **2.25** in dimethylformamide containing potassium carbonate, to yield the ester amidate product **2.26**.

20 Using these procedures, but employing, in place of ethyl N-methyl tyrosinate **2.23** or phenol **2.25**, the aminoesters **1.9** and/or the hydroxy compounds  $R^3OH$ , the corresponding products **2.3** are obtained.

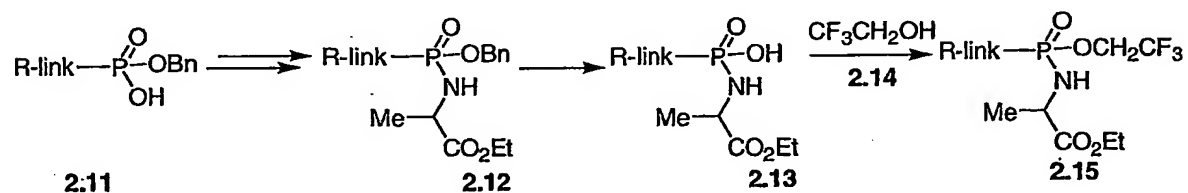
Scheme 2



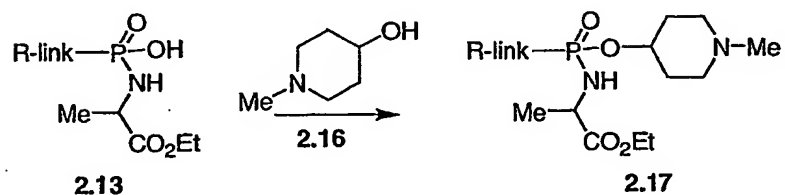
Scheme 2 Example 1



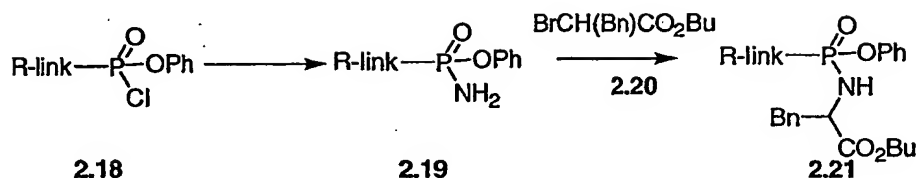
Scheme 2 Example 2



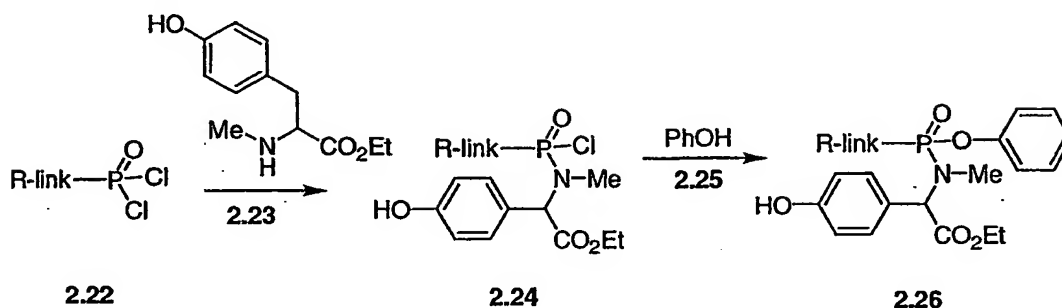
Scheme 2 Example 3



## Scheme 2 Example 4



## Scheme 2 Example 5



Scheme 3 illustrates methods for the preparation of carboalkoxy-substituted phosphonate diesters in which one of the ester groups incorporates a carboalkoxy substituent.

- 5 In one procedure, a phosphonate monoester 1.1, prepared as described above, is coupled, using one of the methods described above, with a hydroxyester 3.1, in which the groups R<sup>4</sup> and R<sup>5</sup> are as described in Scheme 1. For example, equimolar amounts of the reactants are coupled in the presence of a carbodiimide such as dicyclohexyl carbodiimide, as described in Aust. J. Chem., 1963, 609, optionally in the presence of dimethylaminopyridine, as described
- 10 in Tet., 1999, 55, 12997. The reaction is conducted in an inert solvent at ambient temperature.

- The procedure is illustrated in Scheme 3, Example 1. In this method, a monophenyl phosphonate 3.9 is coupled, in dichloromethane solution in the presence of dicyclohexyl
- 15 carbodiimide, with ethyl 3-hydroxy-2-methylpropionate 3.10 to yield the phosphonate mixed diester 3.11.

Using this procedure, but employing, in place of ethyl 3-hydroxy-2-methylpropionate 3.10, different hydroxyesters 3.1, the corresponding products 3.2 are obtained.



The conversion of a phosphonate monoester **1.1** into a mixed diester **3.2** is also accomplished by means of a Mitsunobu coupling reaction with the hydroxyester **3.1**, as described in Org. Lett., 2001, 643. In this method, the reactants **1.1** and **3.1** are combined in a polar solvent such as tetrahydrofuran, in the presence of a triarylphosphine and a dialkyl azodicarboxylate, to give the mixed diester **3.2**. The R<sup>1</sup> substituent is varied by cleavage, using the methods described previously, to afford the monoacid product **3.3**. The product is then coupled, for example using methods described above, with the hydroxy compound R<sup>3</sup>OH, to give the diester product **3.4**.

10 The procedure is illustrated in Scheme 3, Example 2. In this method, a monoallyl phosphonate **3.12** is coupled in tetrahydrofuran solution, in the presence of triphenylphosphine and diethylazodicarboxylate, with ethyl lactate **3.13** to give the mixed diester **3.14**. The product is reacted with tris(triphenylphosphine) rhodium chloride (Wilkinson catalyst) in acetonitrile, as described previously, to remove the allyl group and  
15 produce the monoacid product **3.15**. The latter compound is then coupled, in pyridine solution at ambient temperature, in the presence of dicyclohexyl carbodiimide, with one molar equivalent of 3-hydroxypyridine **3.16** to yield the mixed diester **3.17**.

Using the above procedures, but employing, in place of the ethyl lactate **3.13** or 3-hydroxypyridine, a different hydroxyester **3.1** and/or a different hydroxy compound R<sup>3</sup>OH, the corresponding products **3.4** are obtained.

The mixed diesters **3.2** are also obtained from the monoesters **1.1** via the intermediacy of the activated monoesters **3.5**. In this procedure, the monoester **1.1** is converted into the activated  
25 compound **3.5** by reaction with, for example, phosphorus pentachloride, as described in J. Org. Chem., 2001, 66, 329, or with thionyl chloride or oxalyl chloride (Lv = Cl), or with triisopropylbenzenesulfonyl chloride in pyridine, as described in Nucleosides and Nucleotides, 2000, 19, 1885, or with carbonyl diimidazole, as described in J. Med. Chem., 2002, 45, 1284. The resultant activated monoester is then reacted with the hydroxyester **3.1**,  
30 as described above, to yield the mixed diester **3.2**.

The procedure is illustrated in Scheme 3, Example 3. In this sequence, a monophenyl phosphonate **3.9** is reacted, in acetonitrile solution at 70°C, with ten equivalents of thionyl

chloride, so as to produce the phosphoryl chloride 3.19. The product is then reacted with ethyl 4-carbamoyl-2-hydroxybutyrate 3.20 in dichloromethane containing triethylamine, to give the mixed diester 3.21.

- 5 Using the above procedures, but employing, in place of ethyl 4-carbamoyl-2-hydroxybutyrate 3.20, different hydroxyesters 3.1, the corresponding products 3.2 are obtained.

- The mixed phosphonate diesters are also obtained by an alternative route for incorporation of the  $R^3O$  group into intermediates 3.3 in which the hydroxyester moiety is already  
10 incorporated. In this procedure, the monoacid intermediate 3.3 is converted into the activated derivative 3.6 in which  $L_v$  is a leaving group such as chloro, imidazole, and the like, as previously described. The activated intermediate is then reacted with the hydroxy compound  $R^3OH$ , in the presence of a base, to yield the mixed diester product 3.4.

- 15 The method is illustrated in Scheme 3, Example 4. In this sequence, the phosphonate monoacid 3.22 is reacted with trichloromethanesulfonyl chloride in tetrahydrofuran containing collidine, as described in J. Med. Chem., 1995, 38, 4648, to produce the trichloromethanesulfonyloxy product 3.23. This compound is reacted with 3-(morpholinomethyl)phenol 3.24 in dichloromethane containing triethylamine, to yield the  
20 mixed diester product 3.25.

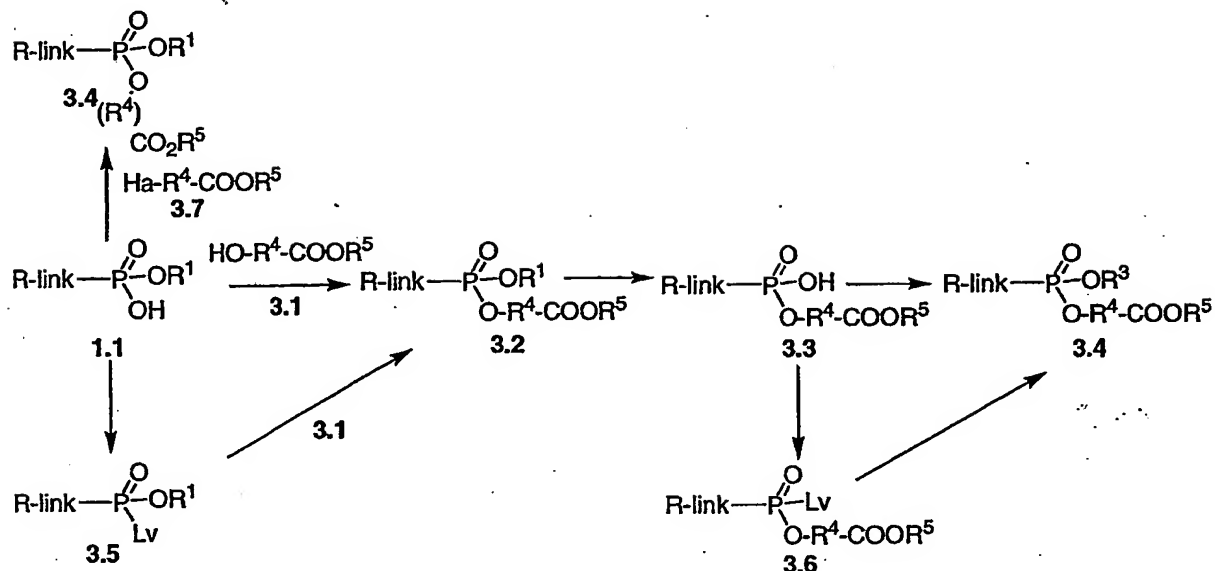
Using the above procedures, but employing, in place of with 3-(morpholinomethyl)phenol 3.24, different carbinols  $R^3OH$ , the corresponding products 3.4 are obtained.

- 25 The phosphonate esters 3.4 are also obtained by means of alkylation reactions performed on the monoesters 1.1. The reaction between the monoacid 1.1 and the haloester 3.7 is performed in a polar solvent in the presence of a base such as diisopropylethylamine, as described in Anal. Chem., 1987, 59, 1056, or triethylamine, as described in J. Med. Chem., 1995, 38, 1372, or in a non-polar solvent such as benzene, in the presence of 18-crown-6, as  
30 described in Syn. Comm., 1995, 25, 3565.

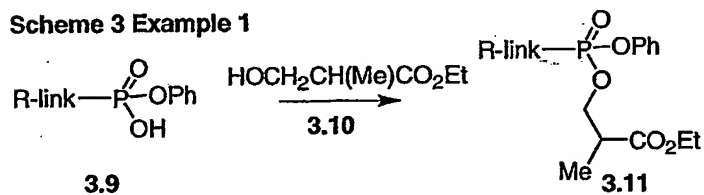
The method is illustrated in Scheme 3, Example 5. In this procedure, the monoacid **3.26** is reacted with ethyl 2-bromo-3-phenylpropionate **3.27** and diisopropylethylamine in dimethylformamide at 80°C to afford the mixed diester product **3.28**.

- 5 Using the above procedure, but employing, in place of ethyl 2-bromo-3-phenylpropionate **3.27**, different haloesters **3.7**, the corresponding products **3.4** are obtained.

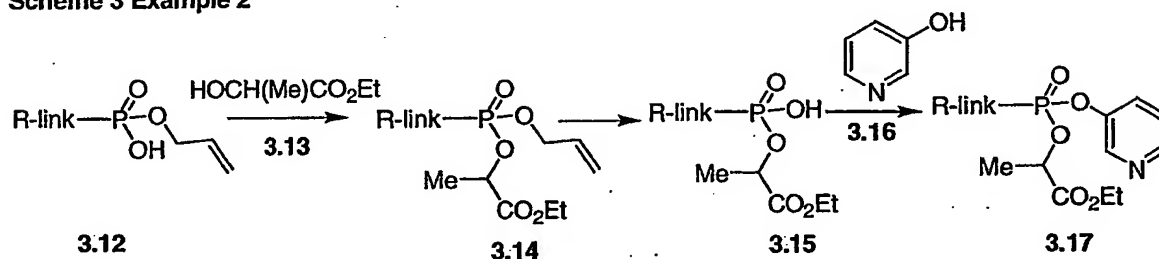
## Scheme 3



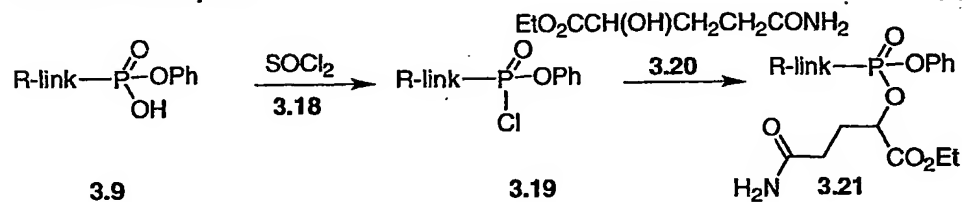
## Scheme 3 Example 1



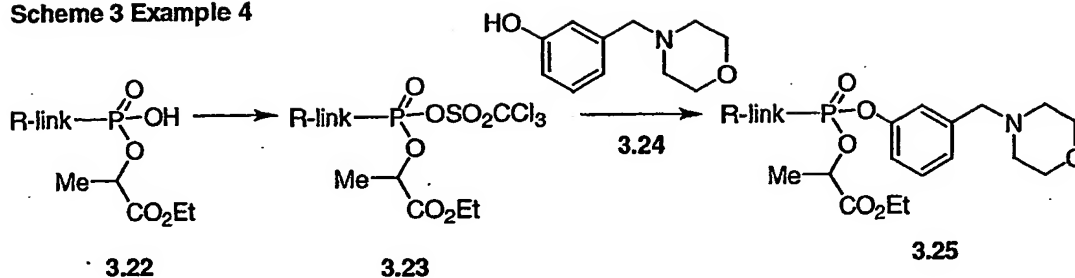
## Scheme 3 Example 2



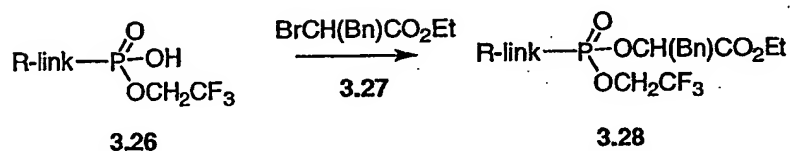
## Scheme 3 Example 3



## Scheme 3 Example 4



## Scheme 3 Example 5



Scheme 4 illustrates methods for the preparation of phosphonate diesters in which both the ester substituents incorporate carboalkoxy groups.

The compounds are prepared directly or indirectly from the phosphonic acids 1.6. In one alternative, the phosphonic acid is coupled with the hydroxyester 4.2, using the conditions described previously in Schemes 1 - 3, such as coupling reactions using dicyclohexyl carbodiimide or similar reagents, or under the conditions of the Mitsunobu reaction, to afford the diester product 4.3 in which the ester substituents are identical.

This method is illustrated in Scheme 4, Example 1. In this procedure, the phosphonic acid 1.6 is reacted with three molar equivalents of butyl lactate 4.5 in the presence of Aldrithiol-2 and triphenyl phosphine in pyridine at ca. 70°C, to afford the diester 4.6. Using the above procedure, but employing, in place of butyl lactate 4.5, different hydroxyesters 4.2, the corresponding products 4.3 are obtained.

Alternatively, the diesters 4.3 are obtained by alkylation of the phosphonic acid 1.6 with a haloester 4.1. The alkylation reaction is performed as described in Scheme 3 for the preparation of the esters 3.4.

This method is illustrated in Scheme 4, Example 2. In this procedure, the phosphonic acid 1.6 is reacted with excess ethyl 3-bromo-2-methylpropionate 4.7 and diisopropylethylamine in dimethylformamide at ca. 80°C, as described in Anal. Chem., 1987, 59, 1056, to produce the diester 4.8.

Using the above procedure, but employing, in place of ethyl 3-bromo-2-methylpropionate 4.7, different haloesters 4.1, the corresponding products 4.3 are obtained.

The diesters 4.3 are also obtained by displacement reactions of activated derivatives 1.7 of the phosphonic acid with the hydroxyesters 4.2. The displacement reaction is performed in a polar solvent in the presence of a suitable base, as described in Scheme 3. The displacement reaction is performed in the presence of an excess of the hydroxyester, to afford the diester product 4.3 in which the ester substituents are identical, or sequentially with limited amounts of different hydroxyesters, to prepare diesters 4.3 in which the ester substituents are different.

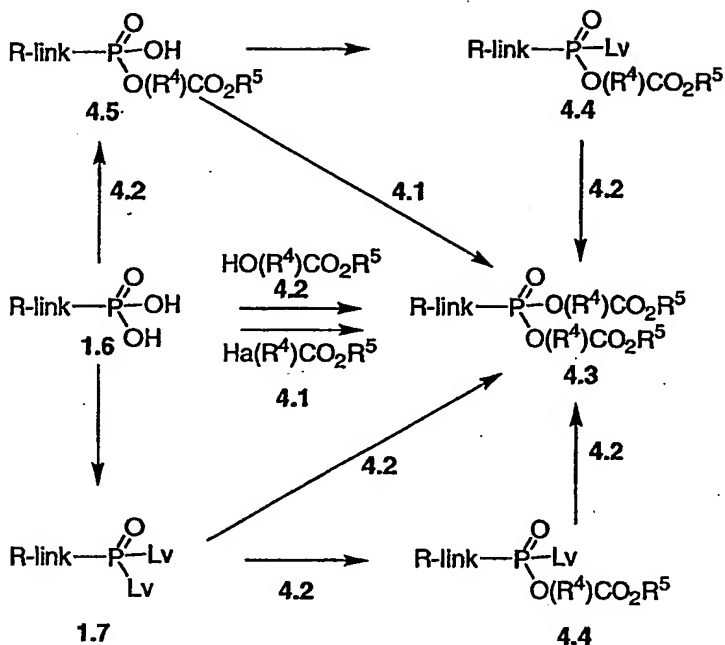
The methods are illustrated in Scheme 4, Examples 3 and 4. As shown in Example 3, the phosphoryl dichloride 2.22 is reacted with three molar equivalents of ethyl 3-hydroxy-2-(hydroxymethyl)propionate 4.9 in tetrahydrofuran containing potassium carbonate, to obtain the diester product 4.10.

Using the above procedure, but employing, in place of ethyl 3-hydroxy-2-(hydroxymethyl)propionate 4.9, different hydroxyesters 4.2, the corresponding products 4.3 are obtained.

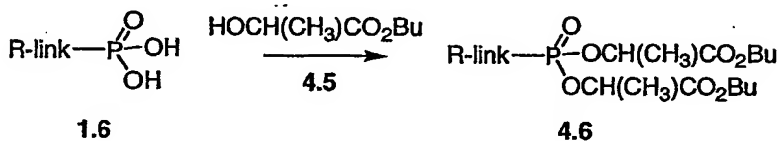
Scheme 4, Example 4 depicts the displacement reaction between equimolar amounts of the phosphoryl dichloride 2.22 and ethyl 2-methyl-3-hydroxypropionate 4.11, to yield the monoester product 4.12. The reaction is conducted in acetonitrile at 70°C in the presence of diisopropylethylamine. The product 4.12 is then reacted, under the same conditions, with one molar equivalent of ethyl lactate 4.13, to give the diester product 4.14.

Using the above procedures, but employing, in place of ethyl 2-methyl-3-hydroxypropionate 4.11 and ethyl lactate 4.13, sequential reactions with different hydroxyesters 4.2, the corresponding products 4.3 are obtained.

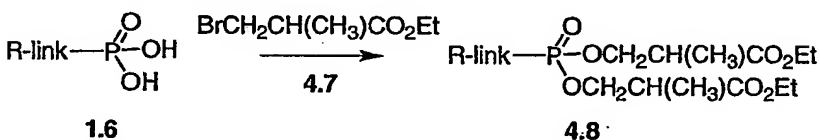
Scheme 4



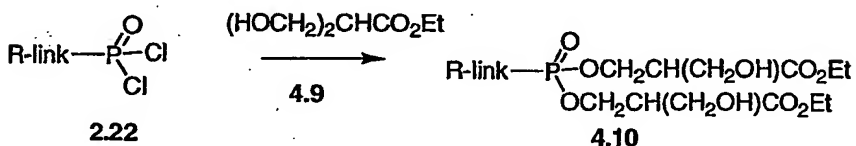
Scheme 4 Example 1



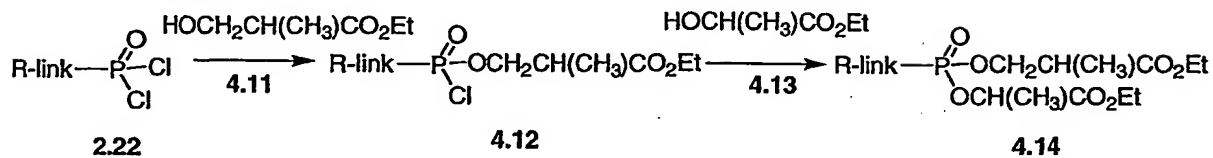
Scheme 4 Example 2



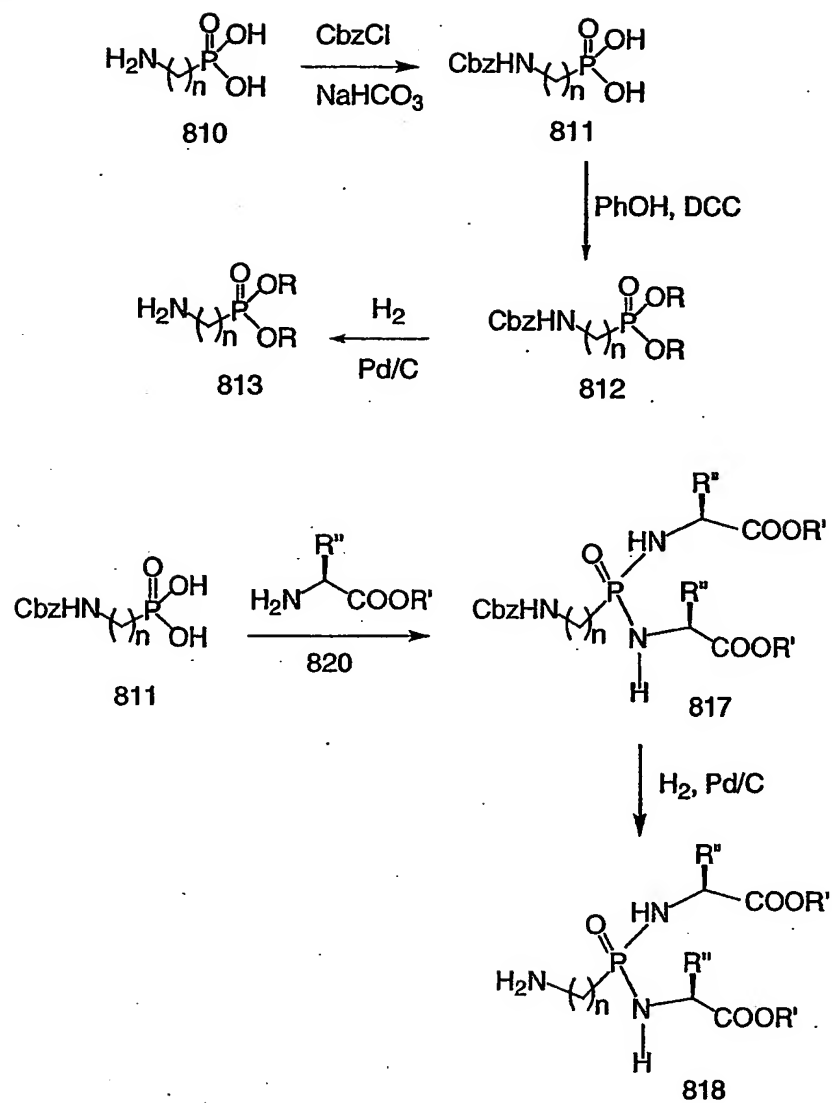
Scheme 4 Example 3



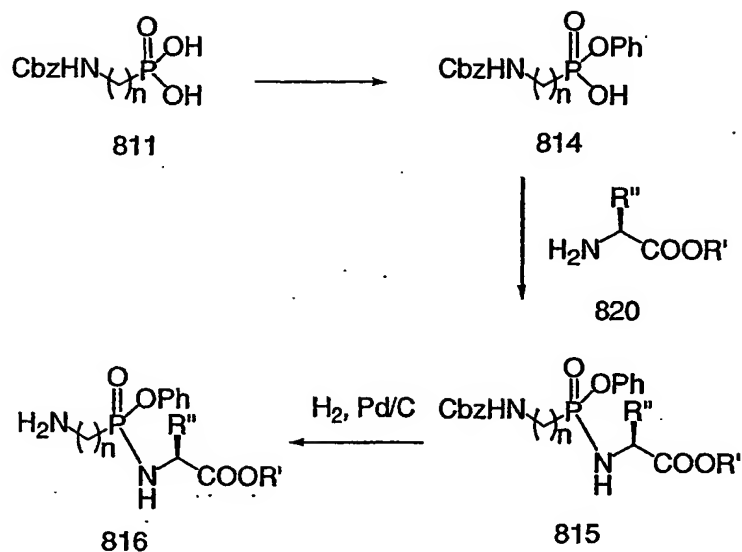
Scheme 4 Example 4



Scheme 1002

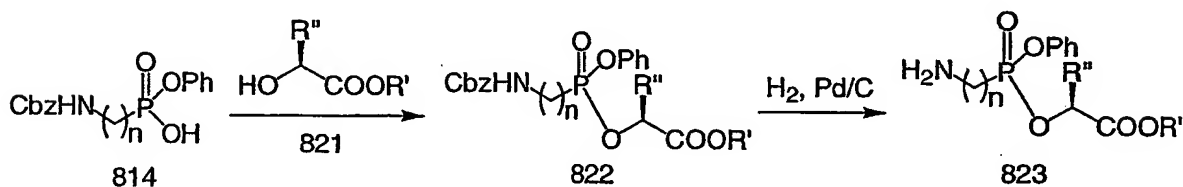




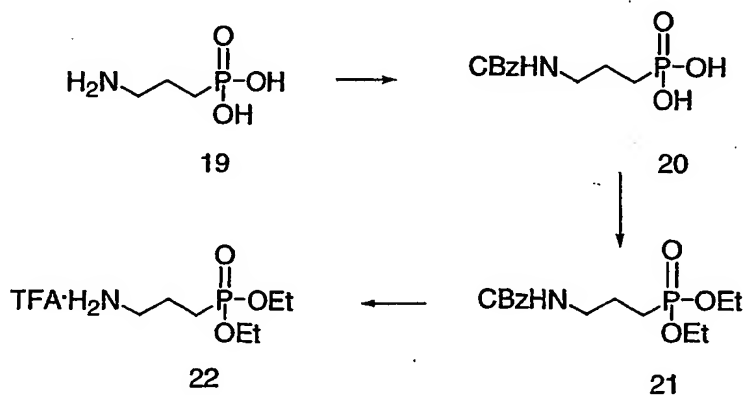


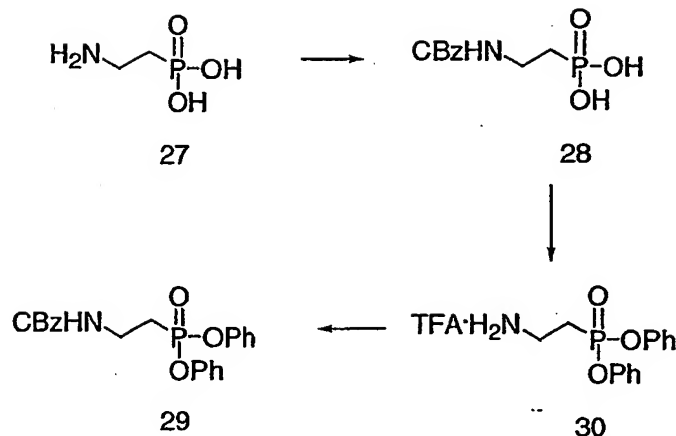
Following the similar procedures, replacement of amino acid esters 820 with lactates 821 (Scheme 1003) provides mono-phosphonic lactates 823. Lactates 823 are useful intermediates to form the phosphonate compounds of the invention.

#### 5 Scheme 1003



#### 10 Scheme 1004



Scheme 1005Example 1

To a solution of 2-aminoethylphosphonic acid (1.26 g, 10.1 mmol) in 2N NaOH (10.1 mL, 20.2 mmol) was added benzyl chloroformate (1.7 mL, 12.1 mmol). After the reaction mixture was stirred for 2 d at room temperature, the mixture was partitioned between Et<sub>2</sub>O and water. The aqueous phase was acidified with 6N HCl until pH = 2. The resulting colorless solid was dissolved in MeOH (75 mL) and treated with Dowex 50WX8-200 (7 g). After the mixture was stirred for 30 minutes, it was filtered and evaporated under reduced pressure to give carbamate **28** (2.37 g, 91%) as a colorless solid (Scheme 1005).

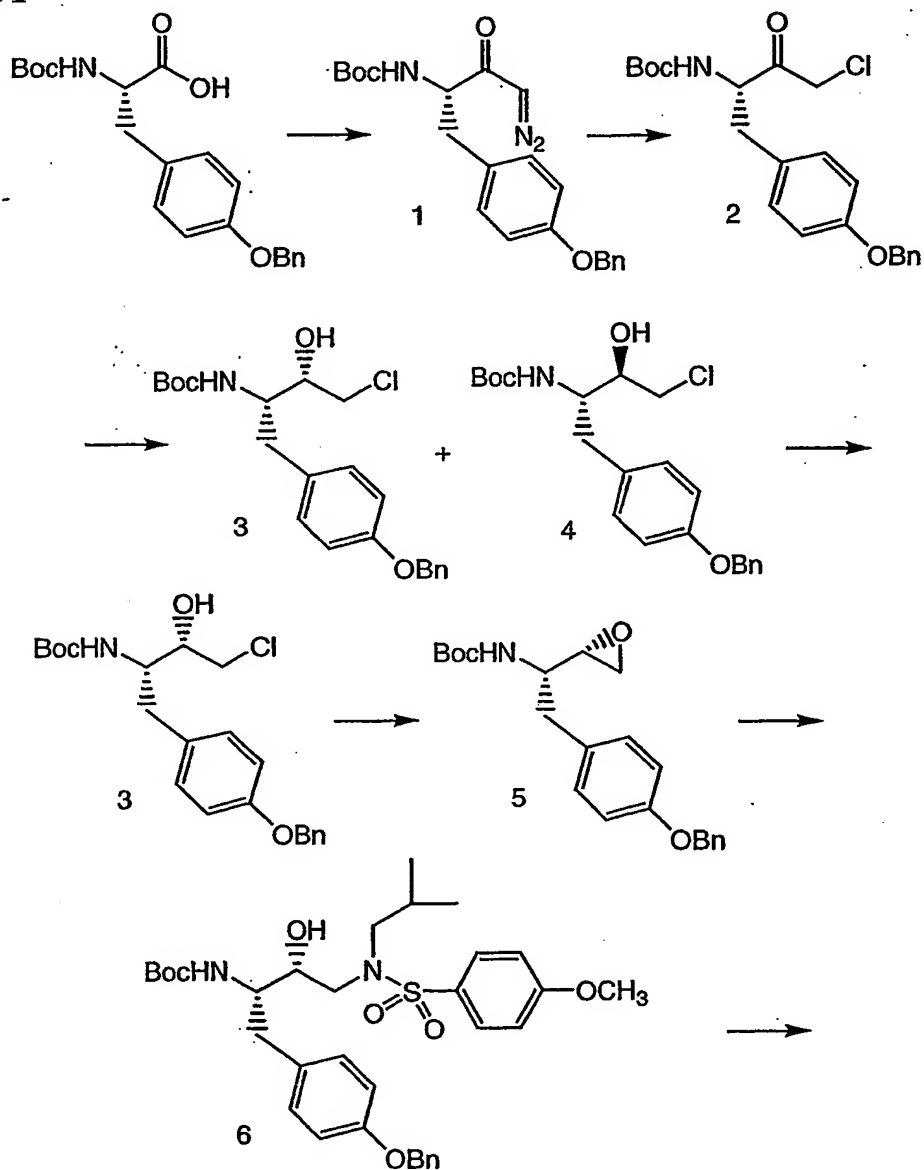
To a solution of carbamate **28** (2.35 g, 9.1 mmol) in pyridine (40 mL) was added phenol (8.53 g, 90.6 mmol) and 1,3-dicyclohexylcarbodiimide (7.47 g, 36.2 mmol). After the reaction mixture was warmed to 70°C and stirred for 5 h, the mixture was diluted with CH<sub>3</sub>CN and filtered. The filtrate was concentrated under reduced pressure and diluted with EtOAc. The organic phase was washed with sat. NH<sub>4</sub>Cl, sat. NaHCO<sub>3</sub>, and brine, then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel twice (eluting 40-60% EtOAc/hexane) to give phosphonate **29** (2.13 g, 57%) as a colorless solid.

To a solution of phosphonate **29** (262 mg, 0.637 mmol) in iPrOH (5 mL) was added TFA (0.05 mL, 0.637 mmol) and 10% Pd/C (26 mg). After the reaction mixture was stirred under H<sub>2</sub> atmosphere (balloon) for 1 h, the mixture was filtered through Celite. The filtrate was evaporated under reduced pressure to give amine **30** (249 mg, 100%) as a colorless oil (Scheme 1005).

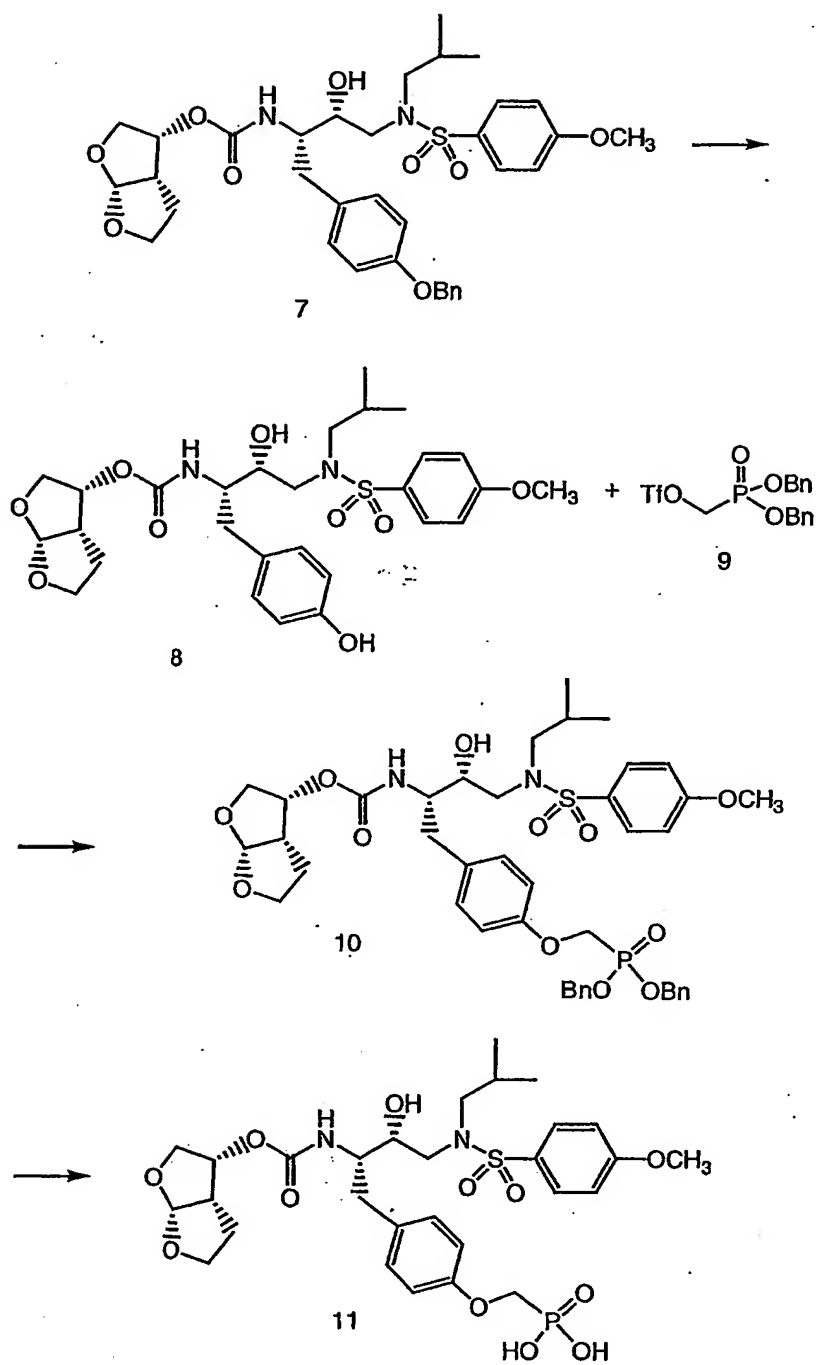
**Scheme Section A**

Exemplary methods of preparing the compounds of the invention are shown in Schemes 1-7 below. A detailed description of the methods is found in the Experimental section below.

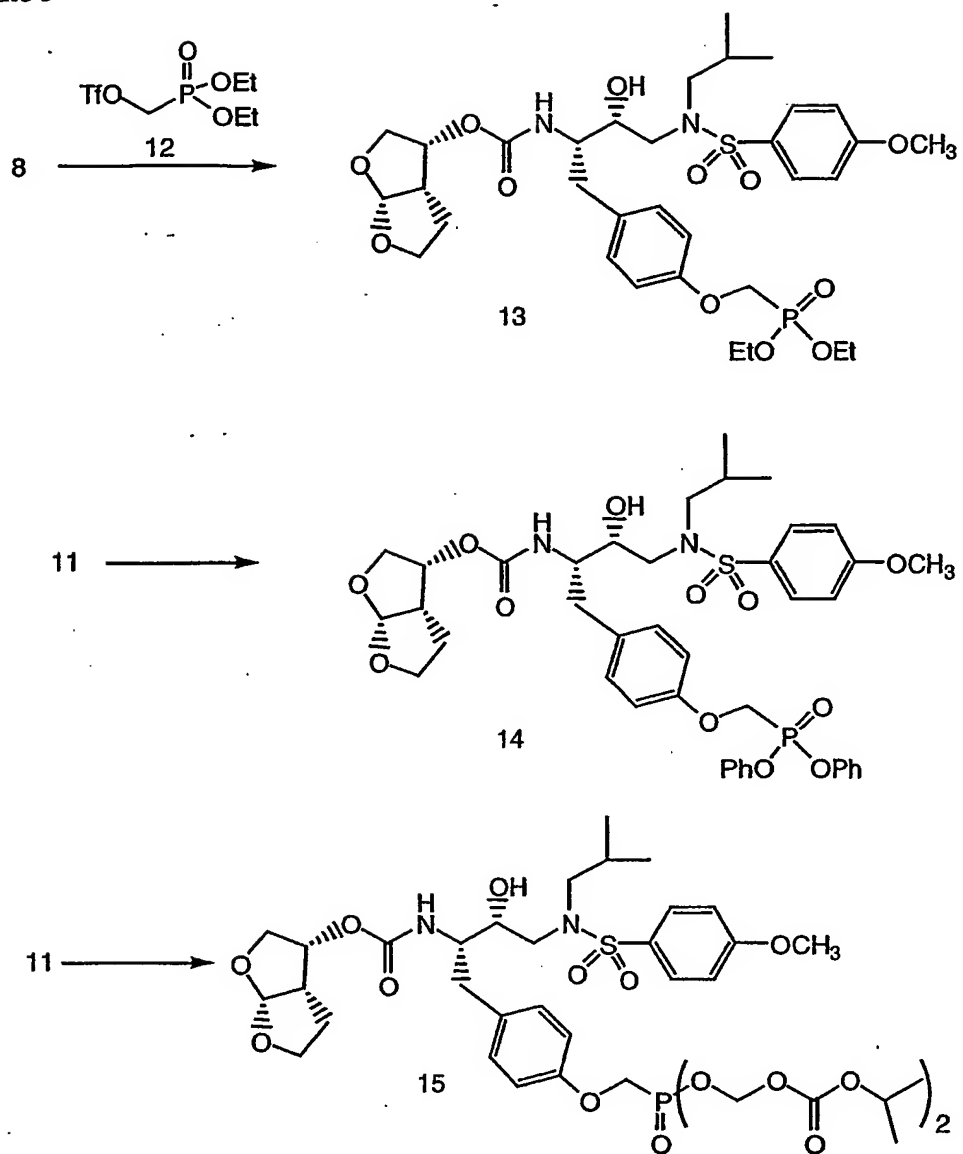
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**Scheme 1**

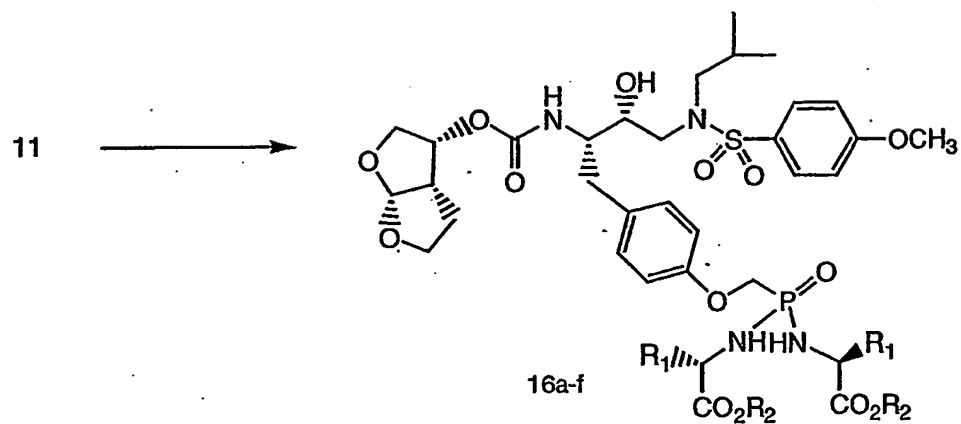
Scheme 2



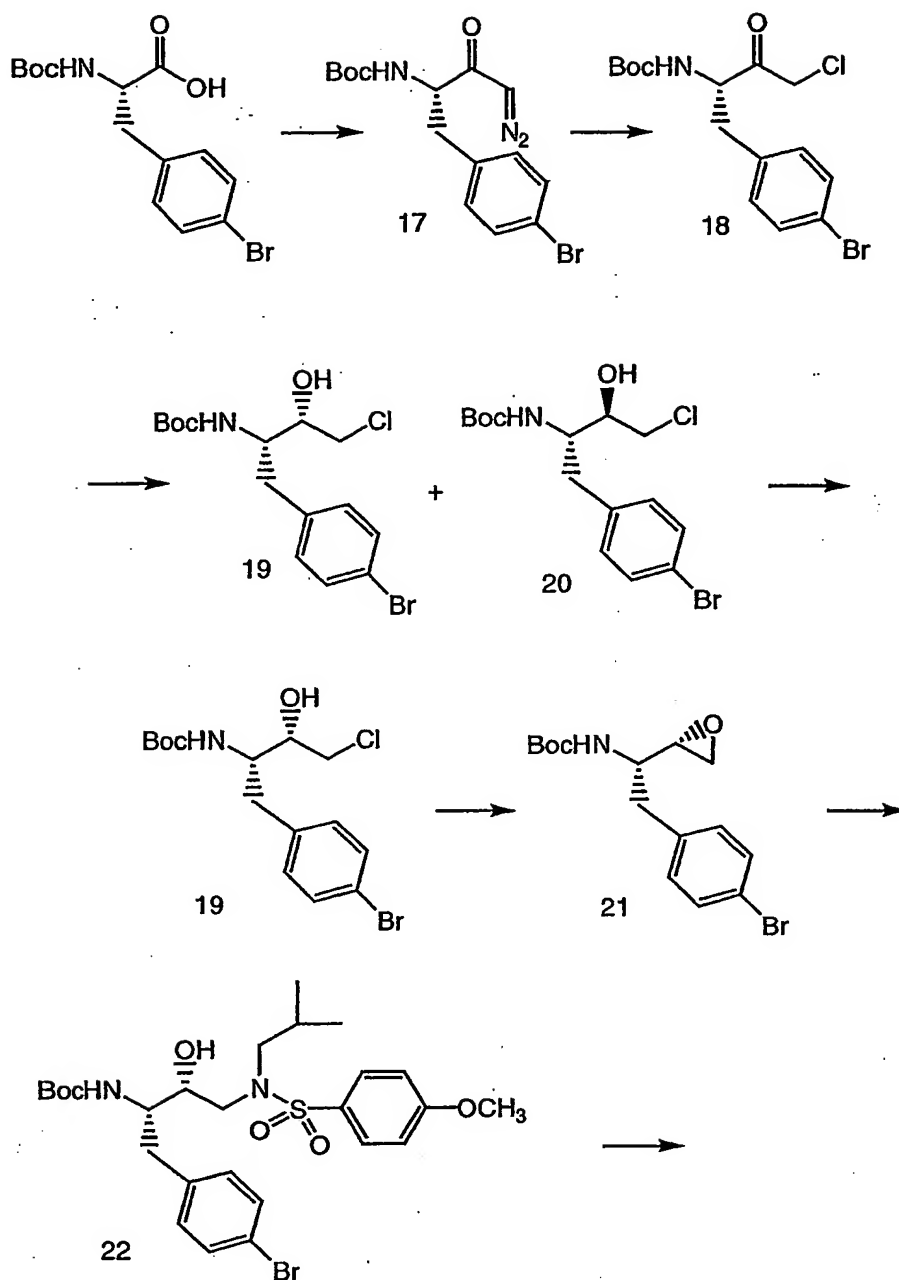
Scheme 3



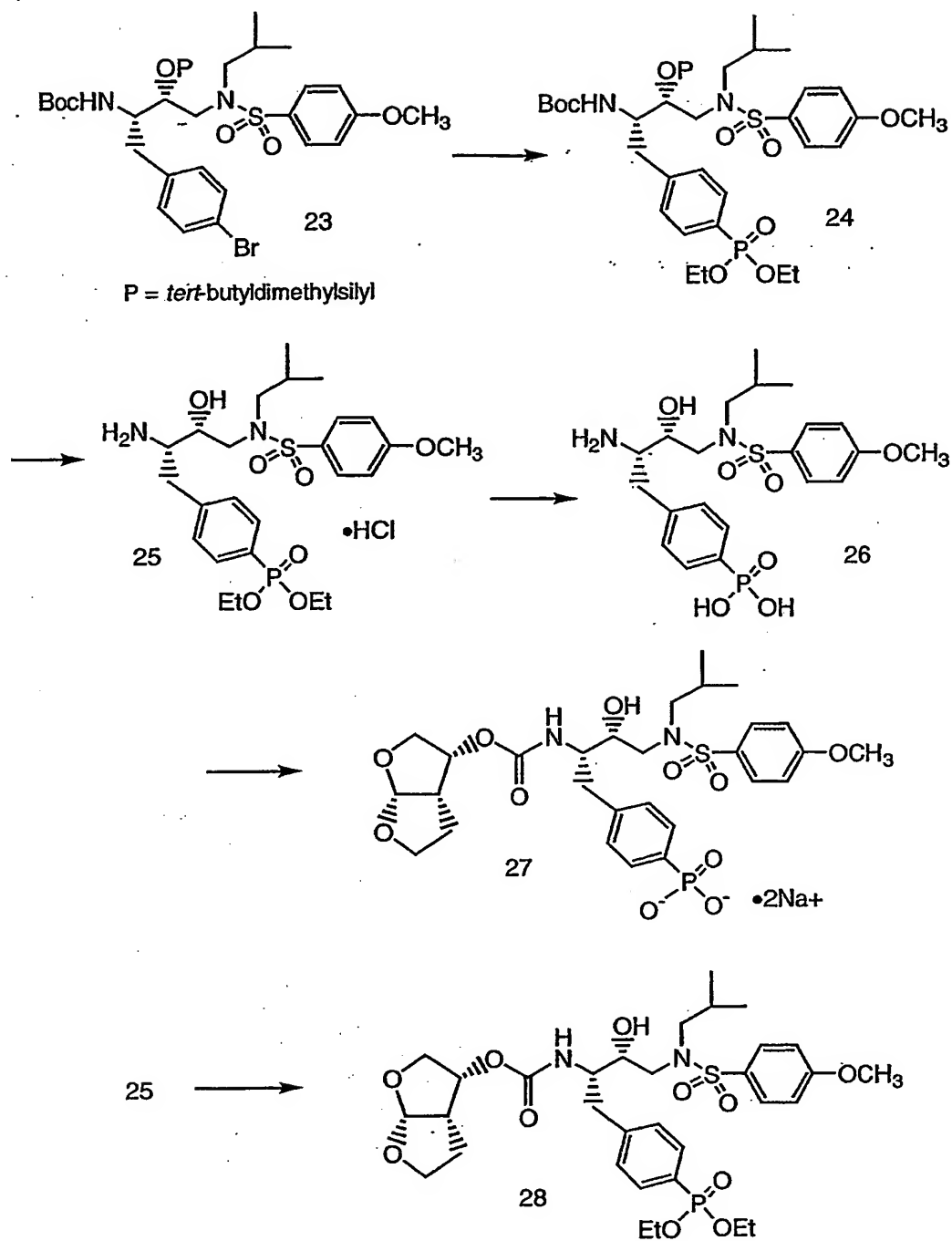
## Scheme 4



Scheme 5

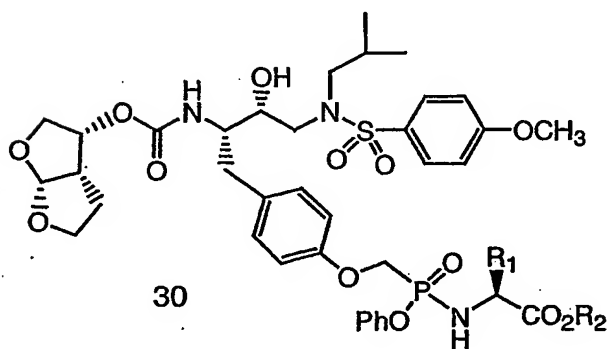
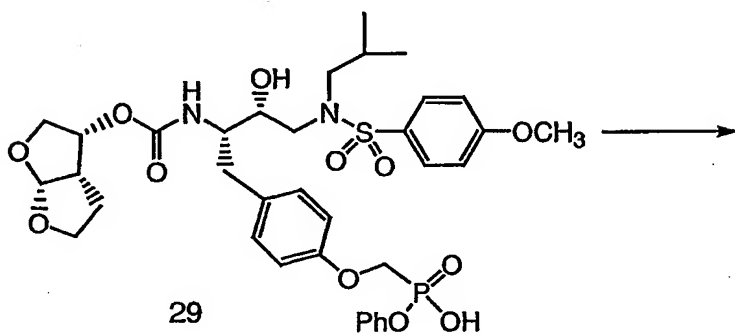
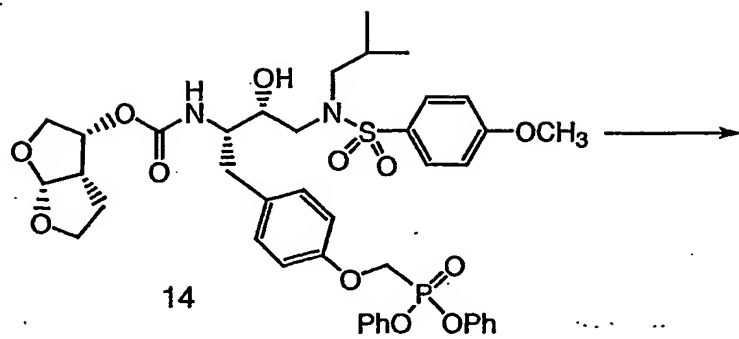


Scheme 6



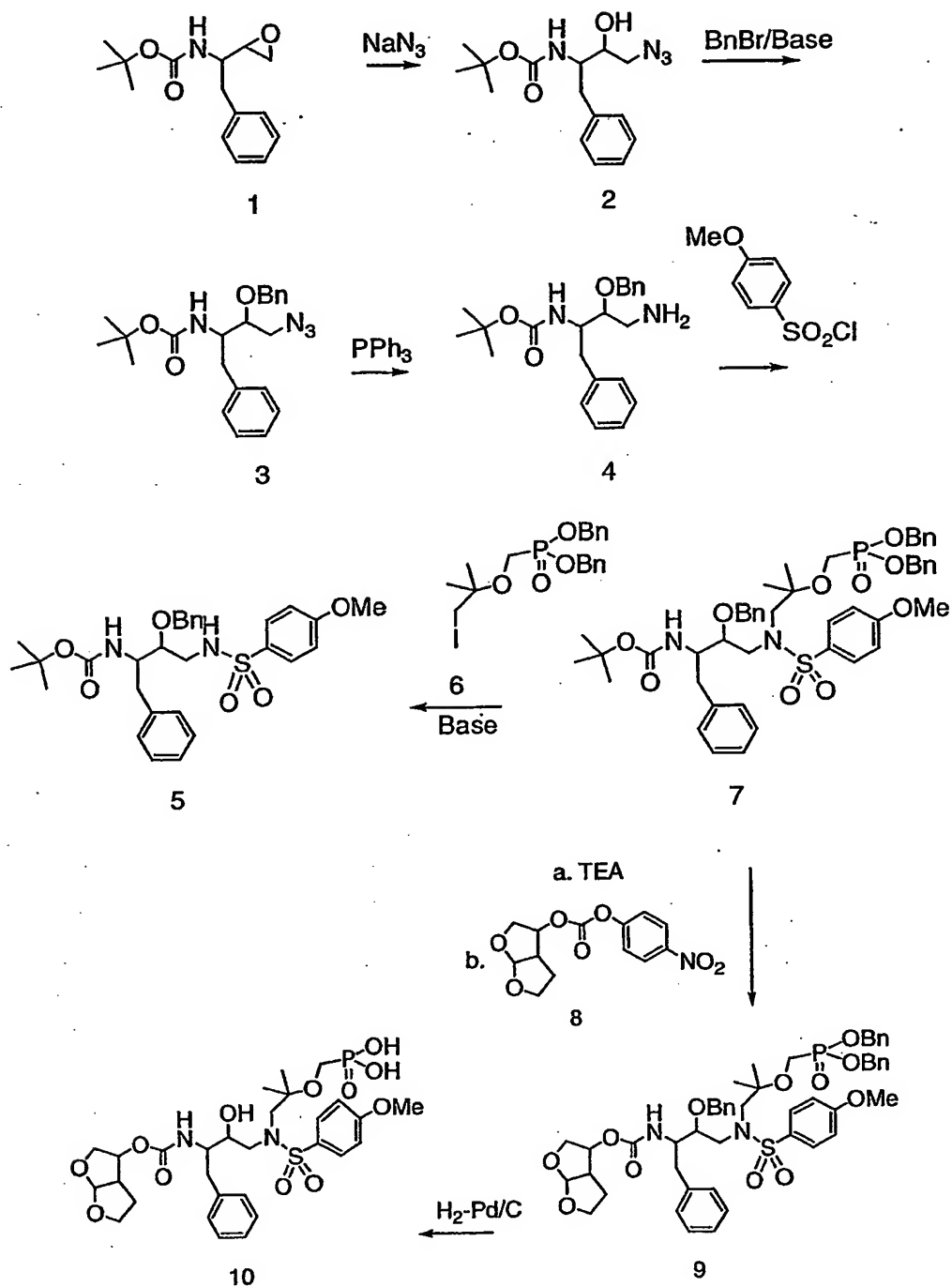


Scheme 7



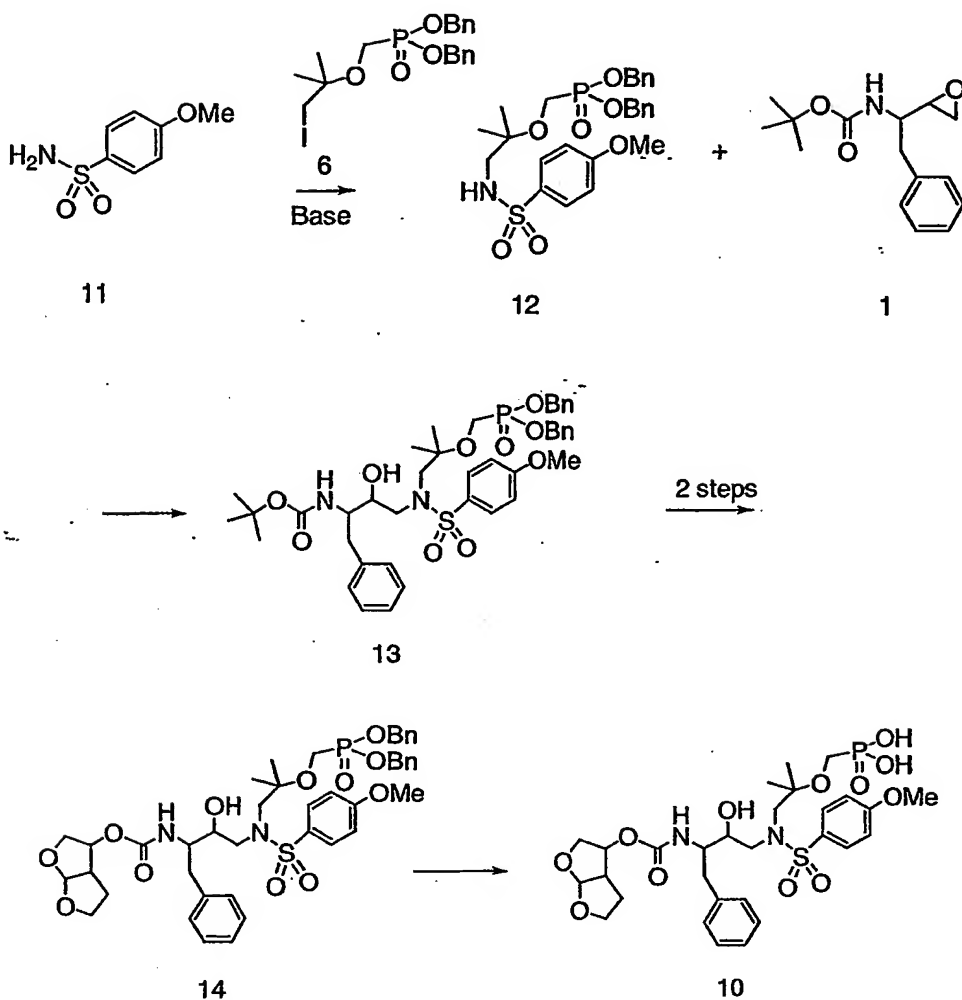
**Scheme Section B**

Alternative exemplary methods of preparing the compounds of the invention are shown in Schemes 101-113 below.

**5 Scheme 101**

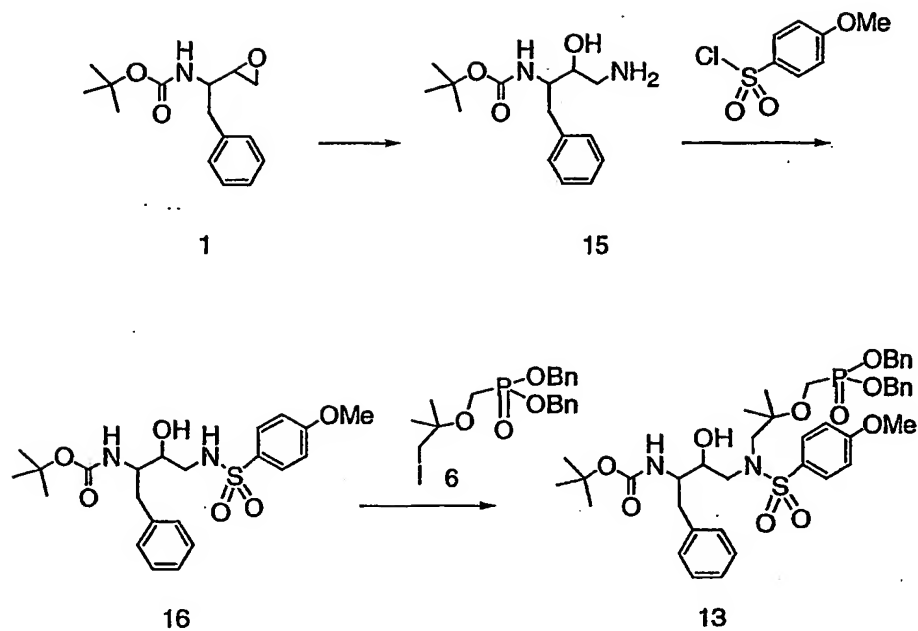
Treatment of commercially available epoxide 1 with sodium azide (Bioorg. & Med. Chem. Lett., 5, 459, 1995) furnishes the azide intermediate 2. The free hydroxyl is converted to benzyl ether 3 by treating it with benzyl bromide in the presence of base such as potassium carbonate. Compound 4 is achieved by the reduction of the azide group with triphenyl phosphine, as described in the publication Bioorg. & Med. Chem. Lett., 7, 1847, 1997. Conversion of the amino group to its sulfonamide derivative 5 is achieved by treating the amine with stoichiometric amounts of sulfonyl chloride. Regioselective alkylation is performed (as shown in the article J. Med. Chem., 40, 2525, 1997) on the sulfonamide nitrogen using the iodide 6 (J. Med. Chem., 35, 2958, 1992) to get the compound 7. Upon TFA catalyzed deprotection of BOC group followed by the reaction with bisfuranyl carbonate 8 (for a similar coupling see, J. Med. Chem., 39, 3278, 1996) furnishes the compound 9. Final deprotection of the protecting groups by catalytic hydrogenolysis result the compound 10.

Scheme 102



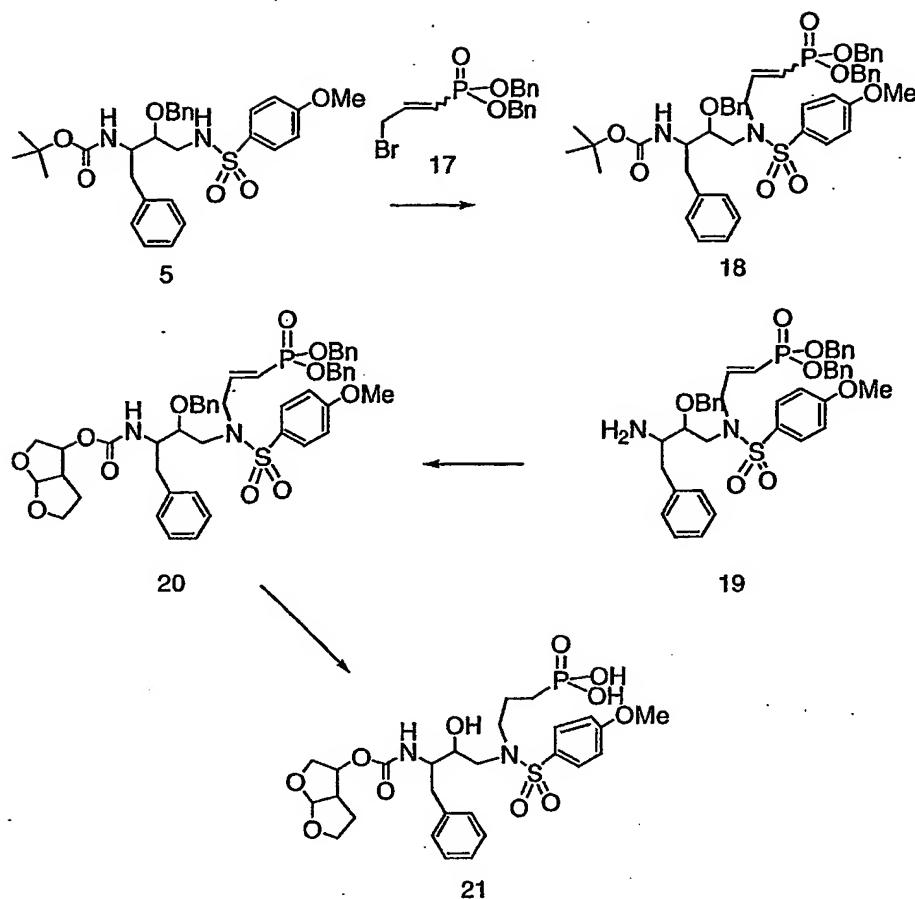
10 The sulfonamide 11 is readily alkylated with the iodide 6 (J. Med. Chem., 35, 2958, 1992) to get the intermediate 12. Regioselective epoxide opening (JP -9124630) of the epoxide 1 with 12 furnishes the intermediate 13. Deprotection of the BOC group followed by the treatment of bisfuranyl carbonate 8 yields the intermediate 14 which is subjected to hydrogenation to furnish the compound 10.

Scheme 103



- 5 The epoxide 1 is converted to the aminohydroxyl derivative 15 using the known procedure (J. Med. Chem., 37, 1758, 1994). Sulfonation of 15 using benzene sulfonylchloride affords the compound 16. Installation of the side chain to get the intermediate 13 is achieved by alkylation of sulfonamide nitrogen with iodide 6. The intermediate 13 is converted to the compound 10 using the same sequence as shown in scheme 102.

Scheme 104

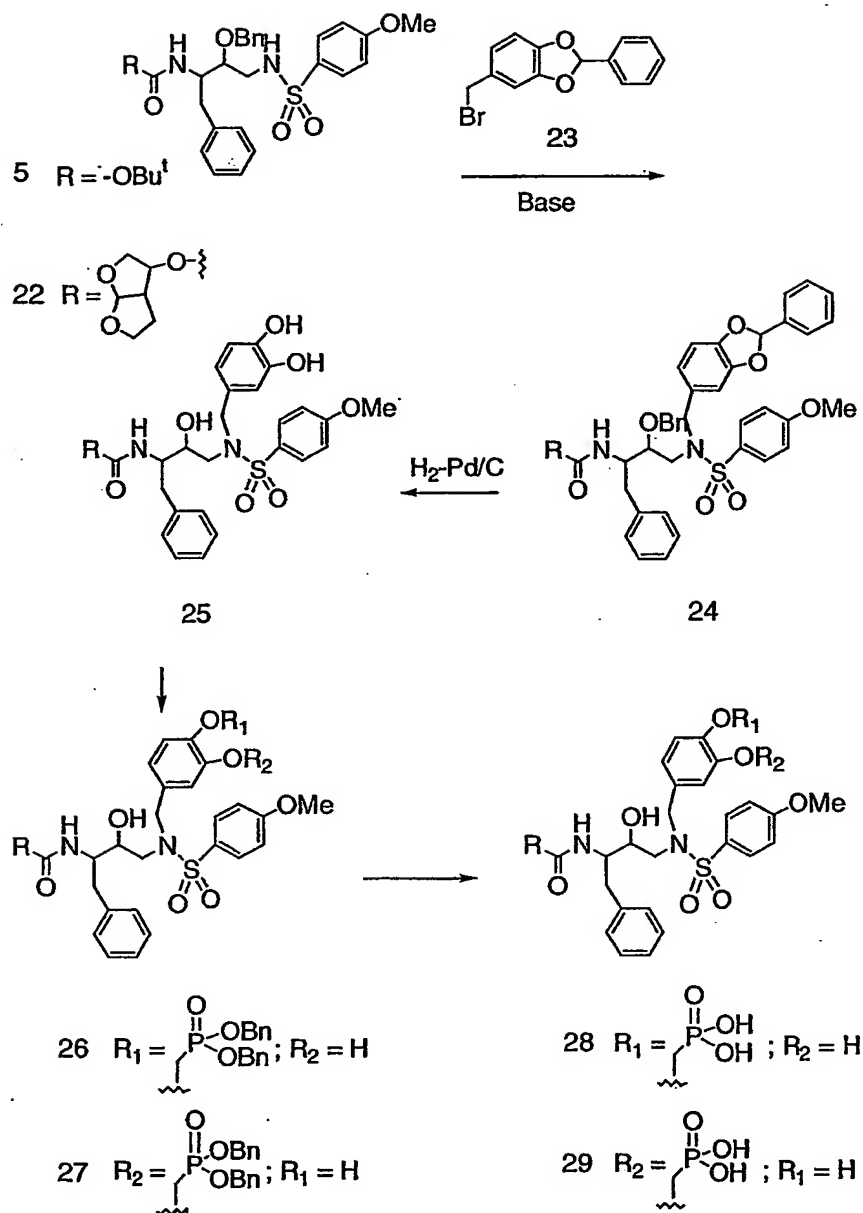


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Sulfonamide 5 is alkylated under basic conditions using the allyl bromide 17 (Chem. Pharm. Bull., 30, 111, 1982) to get the intermediate 18. Similar transformation is reported in literature (J. Med. Chem., 40, 2525, 1997). Hydrolysis of BOC group with TFA and acylation of the resulting amine 19 with bisfuranyl carbonate 8 yields the compound 20.

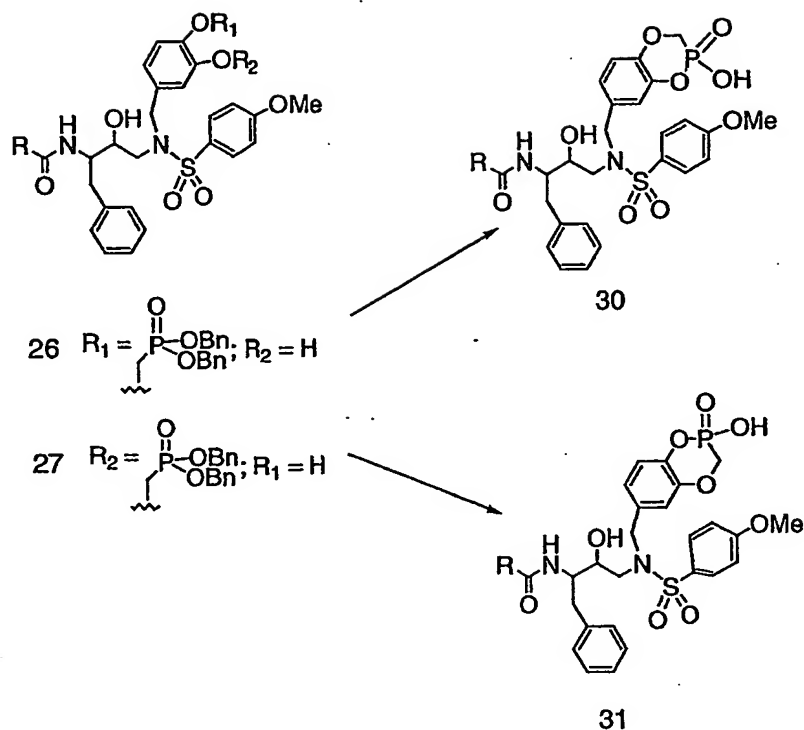
10 Hydrogenation using Pd/C catalysis under H<sub>2</sub> atmosphere affords the phosphonic acid 21.

## Scheme 105



5.

## Scheme 105 (cont)

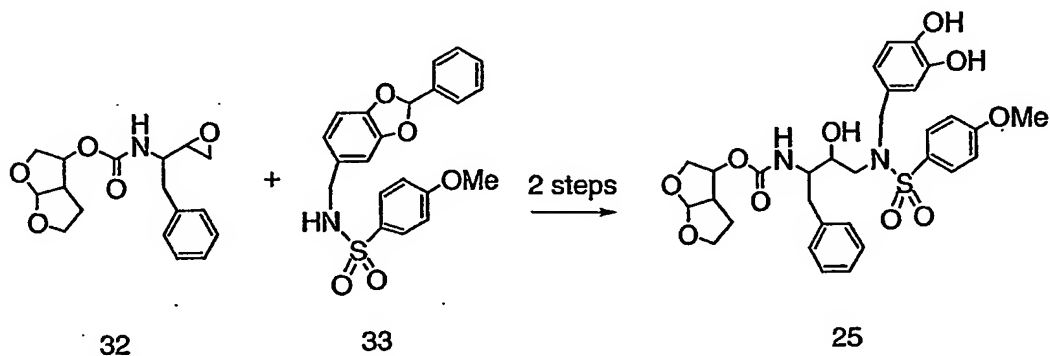


- 5 Sulfonamide 5 is converted to 22 via hydrolysis of BOC group with TFA and acylation with bisfuranyl carbonate 8. The sulfonamide 22 is alkylated with the bromide 23 (J. Med. Chem., 40, 2525, 1997) to get the compound 24, which upon hydrogenolysis gives the catechol 25. Alkylation of the phenolic groups using dibenzylhydroxymethyl phosphonate (J. Org. Chem., 53, 3457, 1988) affords regioisomeric compounds 26 and 27. These compounds 26 and 27
- 10 are hydrogenated to get the phosphonic acids 28 and 29, respectively. Individual cyclic phosphonic acids 30 and 31 are obtained under basic (like NaH) conditions (US 5886179) followed by hydrogenolysis of the dibenzyl ester derivatives 26 and 27.



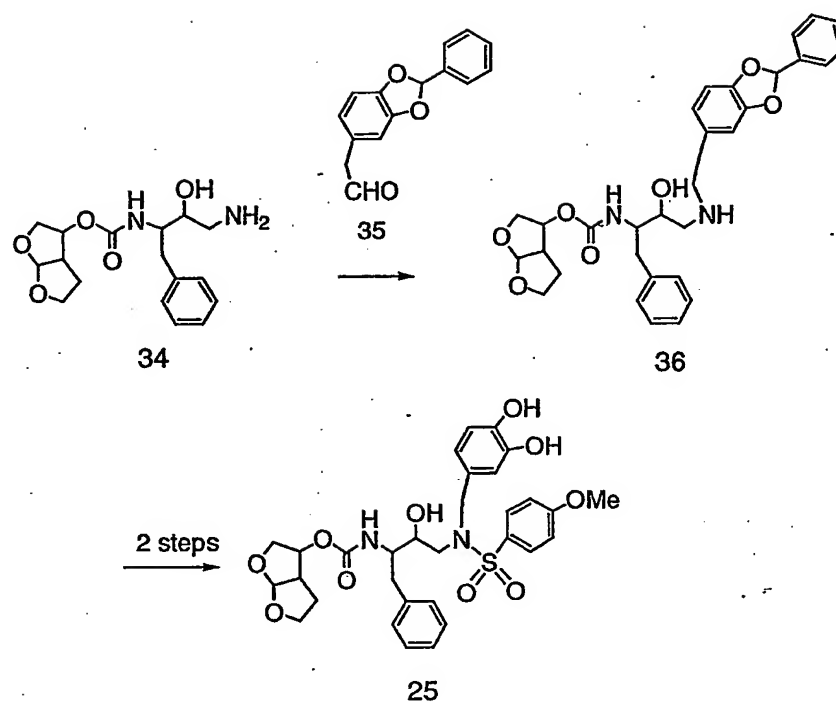
## Scheme 106

In this route, compound 25 is obtained by conducting a reaction between the epoxide 32 and  
5 the sulfonamide 33 using the conditions described in the Japanese Patent No. 9124630.



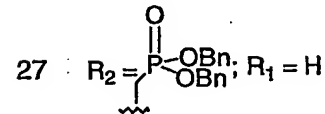
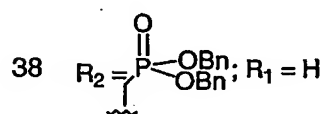
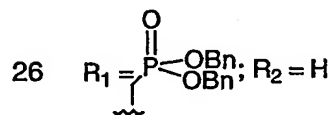
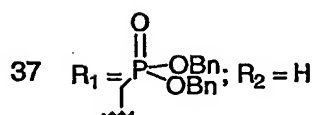
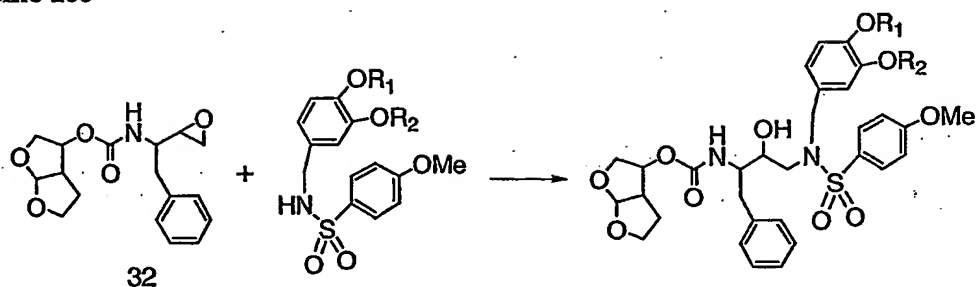
10 Epoxide 32 and sulfonamide 33 are synthesized utilizing similar methodology delineated in the same patent.

Scheme 107



- 5 Compound 34 is obtained from 32 using similar sequence depicted in J. Med. Chem., 37, 1758, 1994. Reductive amination (for similar transformation see WO 00/47551) of compound 34 with aldehyde 35 furnishes the intermediate 36 which is converted to the compound 25 by sulfonation followed by hydrogenation.

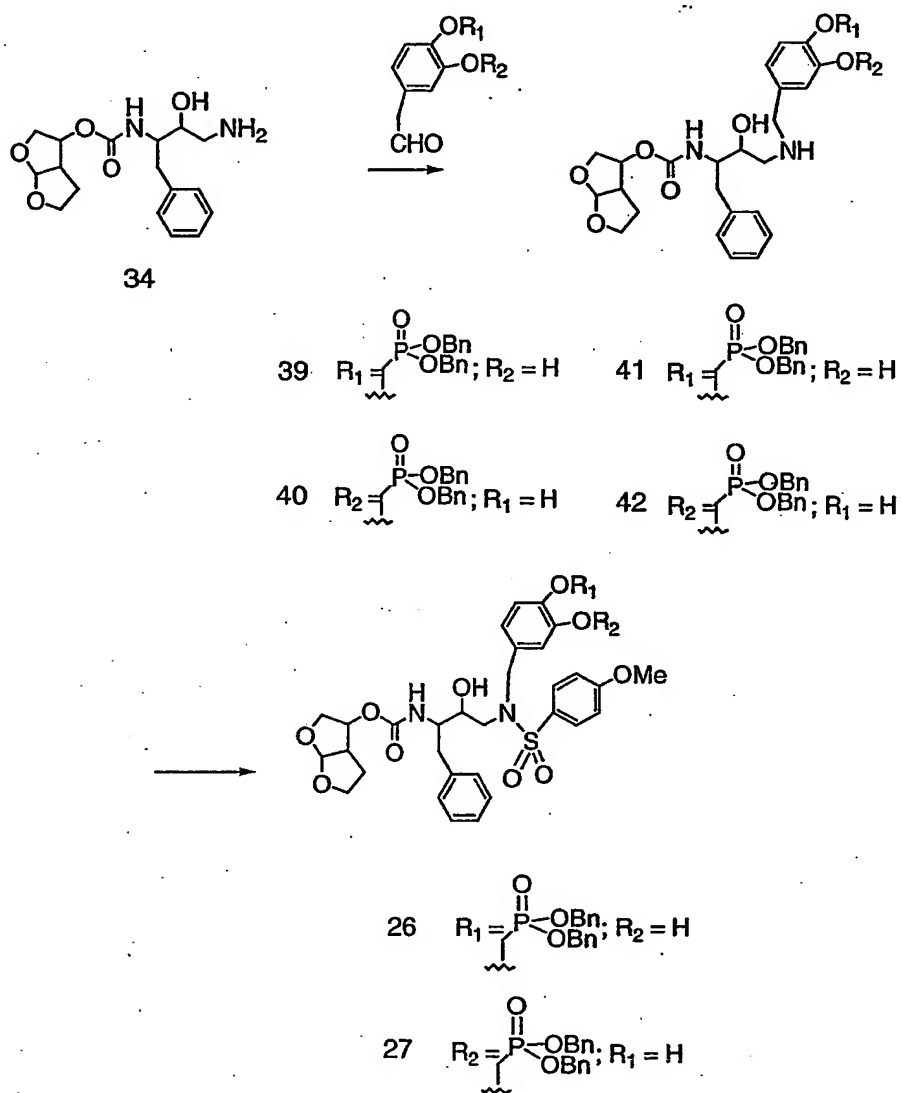
Scheme 108



- 5 Treatment of epoxide 32 with sulfonamides 37 and/or 38 under conditions described in Japanese Patent No. 9124630 furnishes 26 and 27.

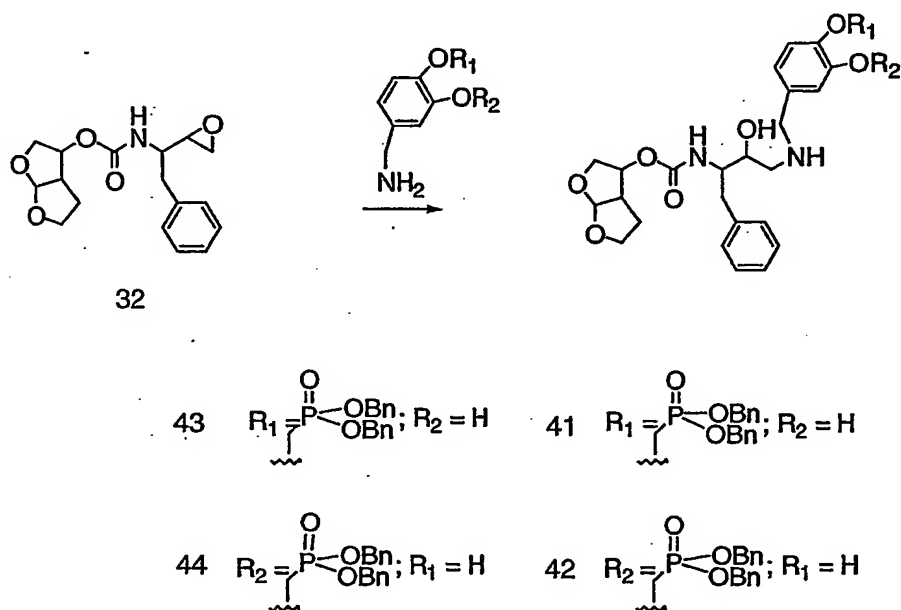
## Scheme 109

Reductive amination of aminohydroxyl intermediate 34 with the aldehydes 39 and 40 as described in patent WO 00/47551, furnish 41 and 42 which undergoes smooth sulfonylation to give 26 and 27.

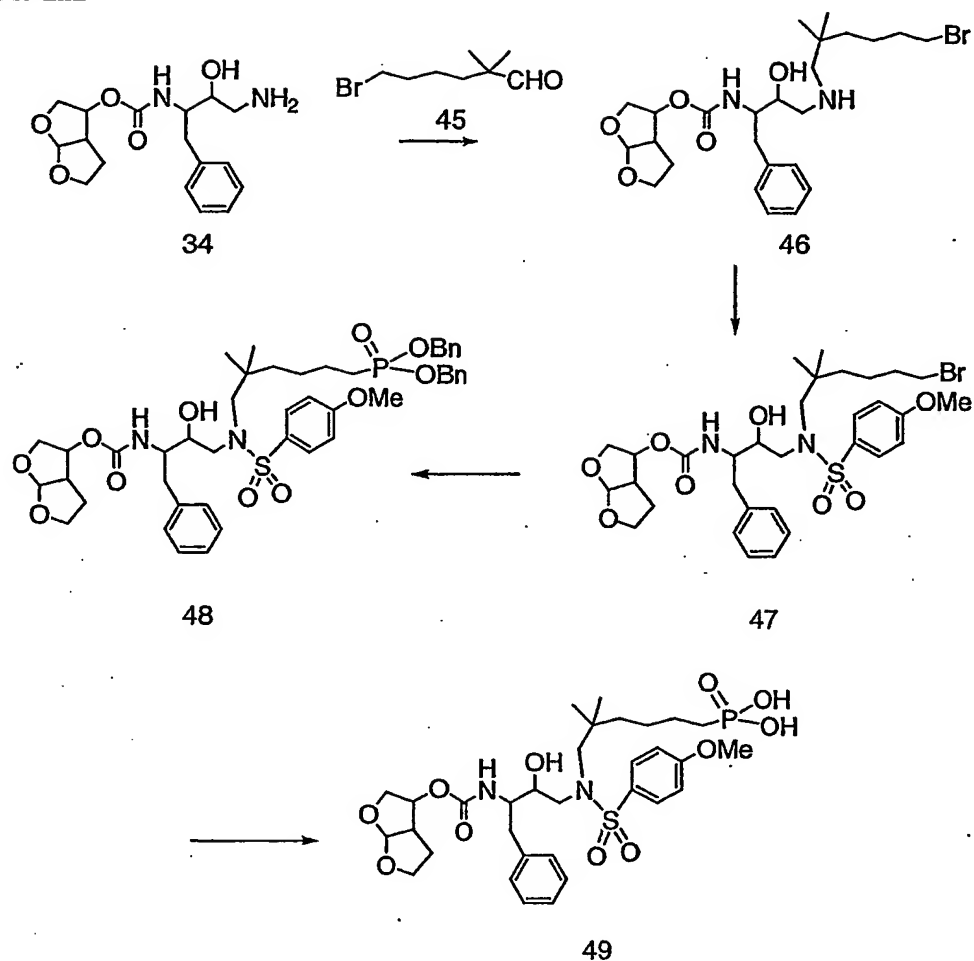


## Scheme 110

In an alternate approach, where epoxide 32 is opened with benzyl amines 43 and 44 under conditions described above furnishes 41 and 42, respectively. Similar transformations were documented in the Japanese Patent No. 9124630.



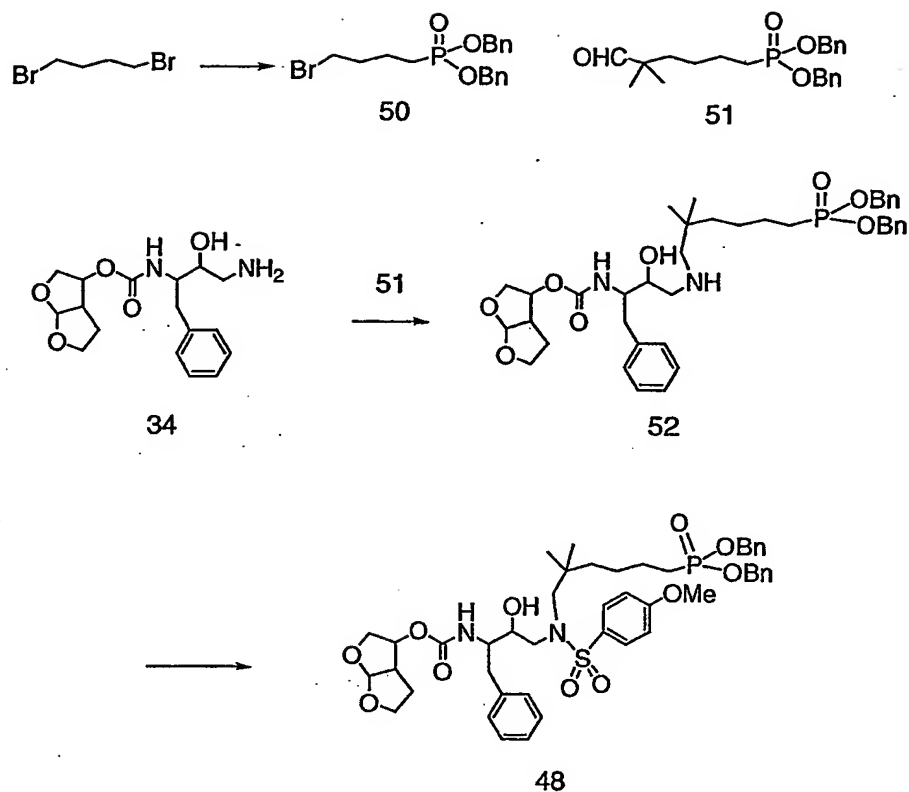
**Scheme 111**



5

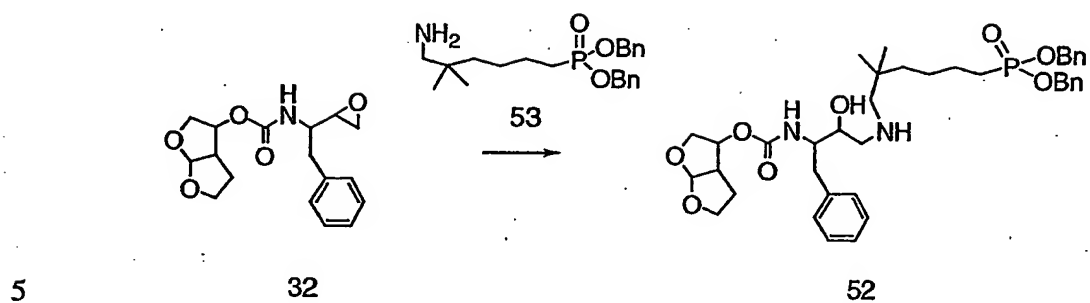
Reductive amination of the bromoaldehyde 45 (J. Organomet. Chem., FR; 122, 123, 1976) with the amine 34 gives 46 which then undergoes sulfonylation to furnish 47. The bromoderivative 47 is converted to the phosphonate 48 under Michaelis-Arbuzov reaction conditions (Bioorg. Med. Chem. Lett., 9, 3069, 1999). Final hydrogenation of 48 delivers the phosphonic acid 49.

## Scheme 112



The intermediate 48 is also obtained as shown in scheme 112. Reductive amination of the aldehyde 52 with the amine 34 offers the phosphonate 52 and sulfonylation of this intermediate furnishes 48.

## Scheme 113

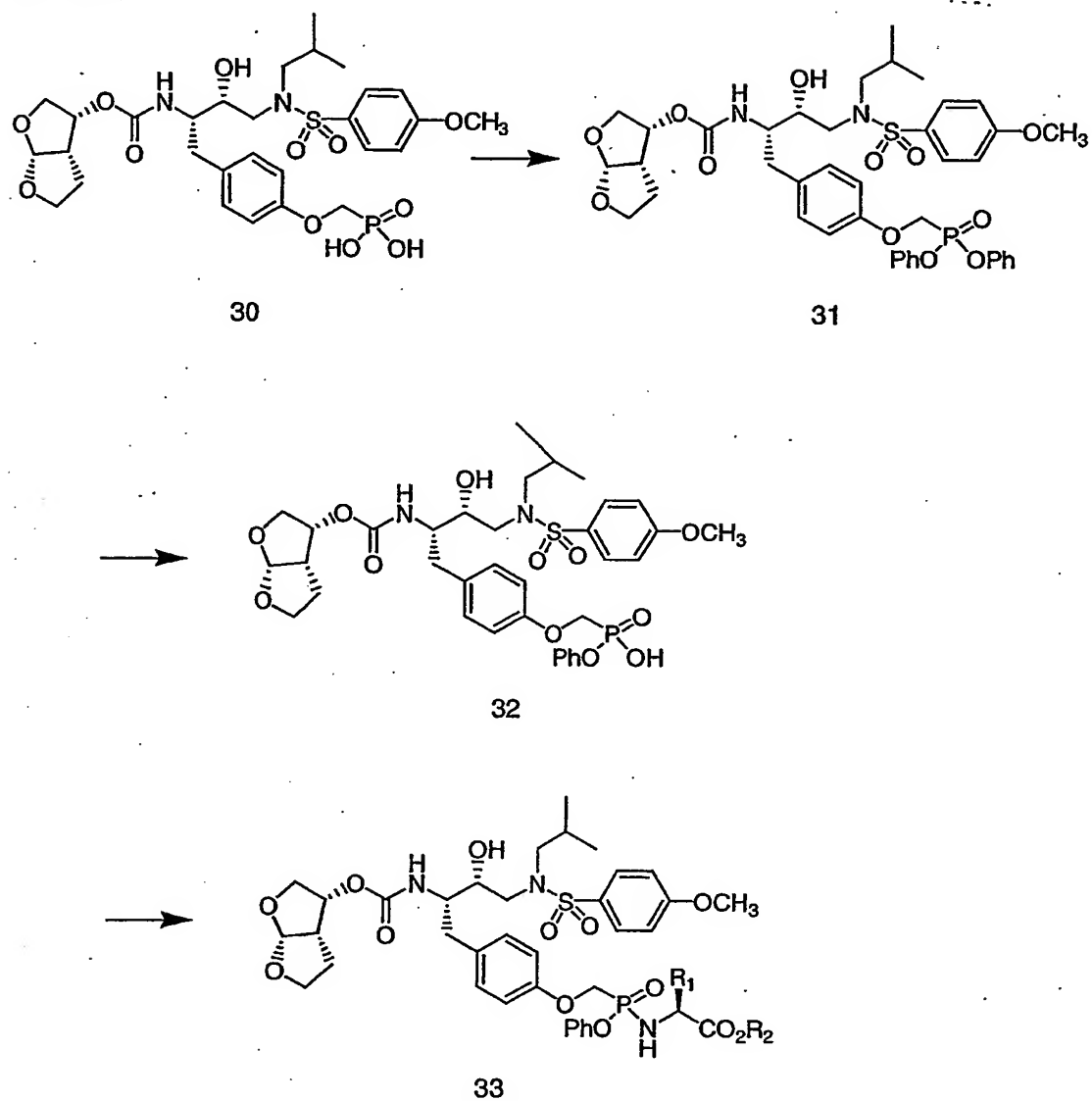


Alternatively, compound 52 is obtained from the epoxide 32 by a ring opening reaction with  
10 the aminophosphonate 53 (Scheme 113).



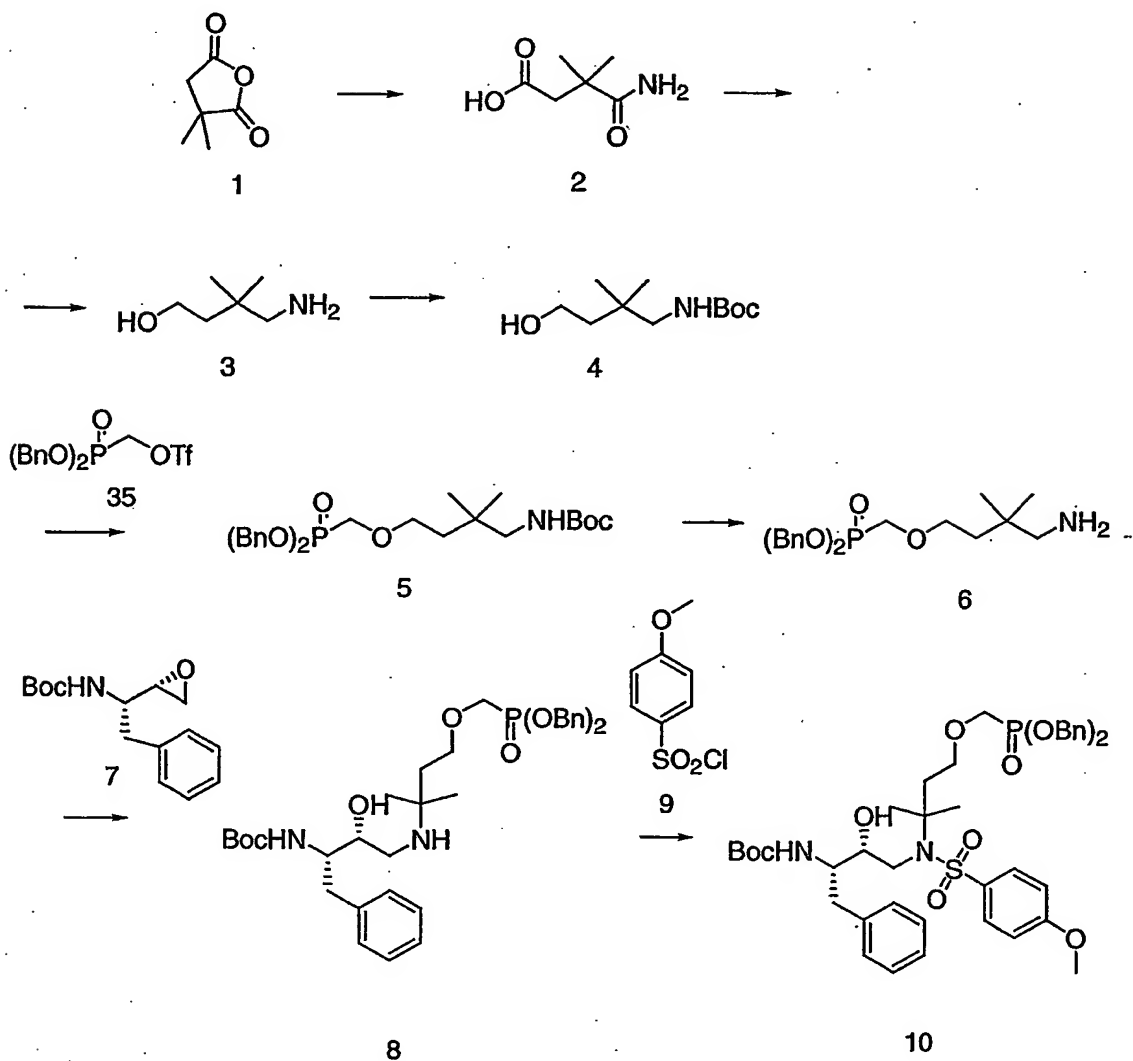
**Scheme Section C**

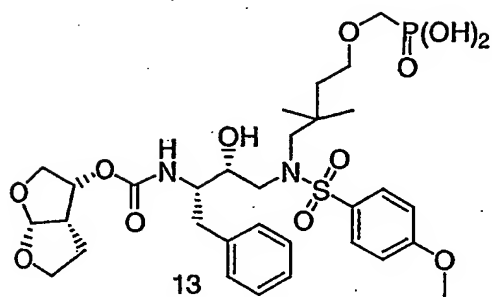
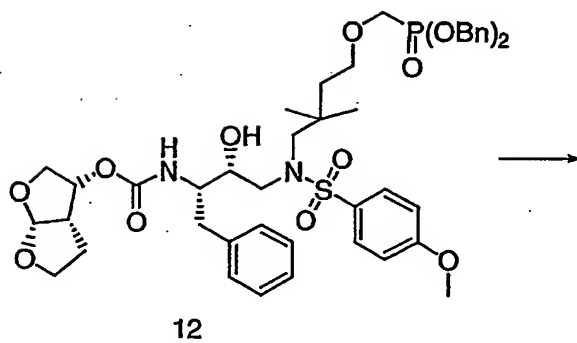
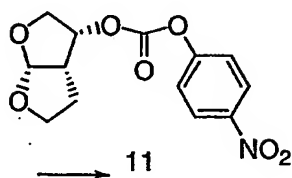
Scheme 9 is described in the Examples.

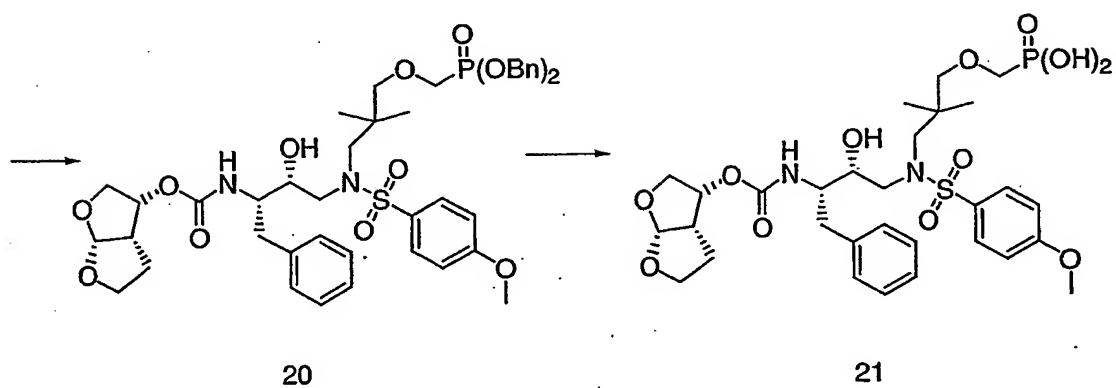
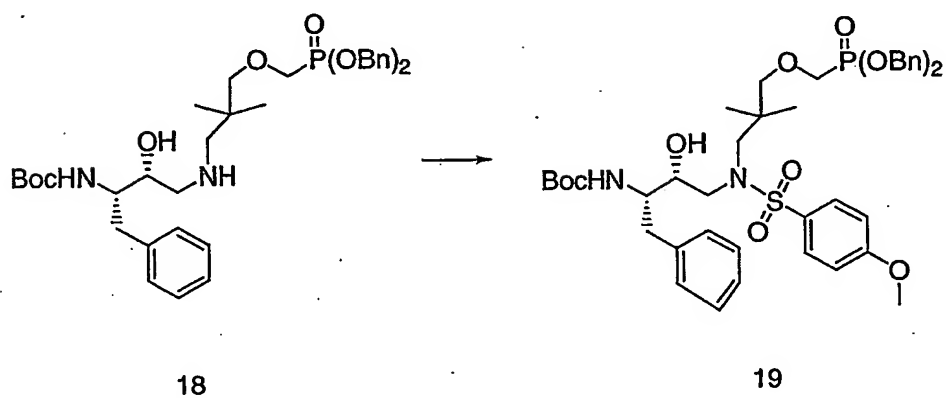
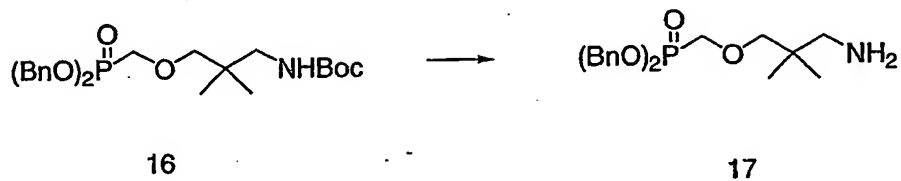
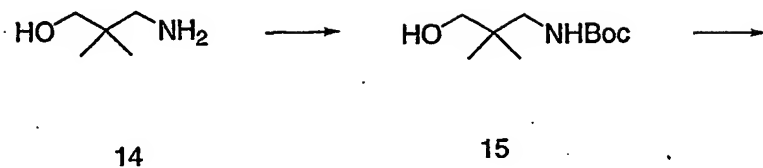
**5 Scheme 9**

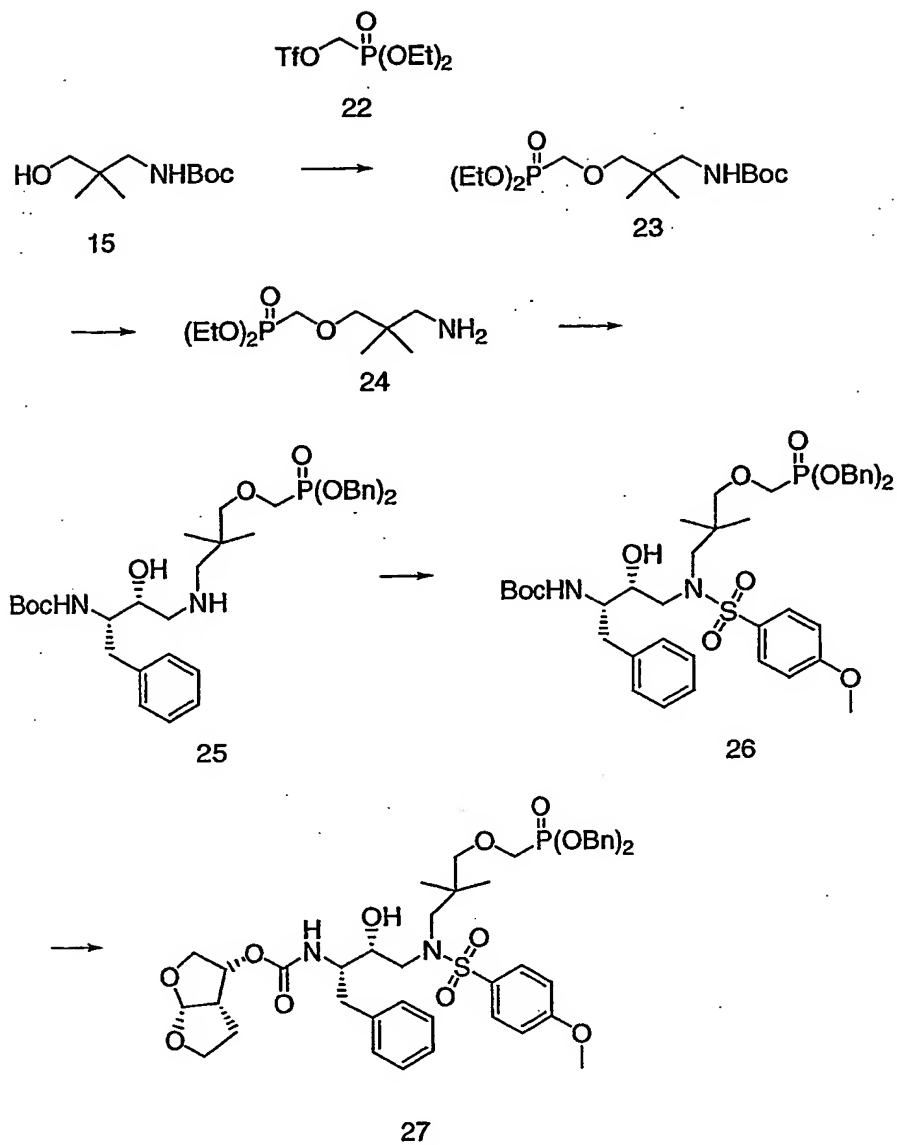
**Scheme Section D**

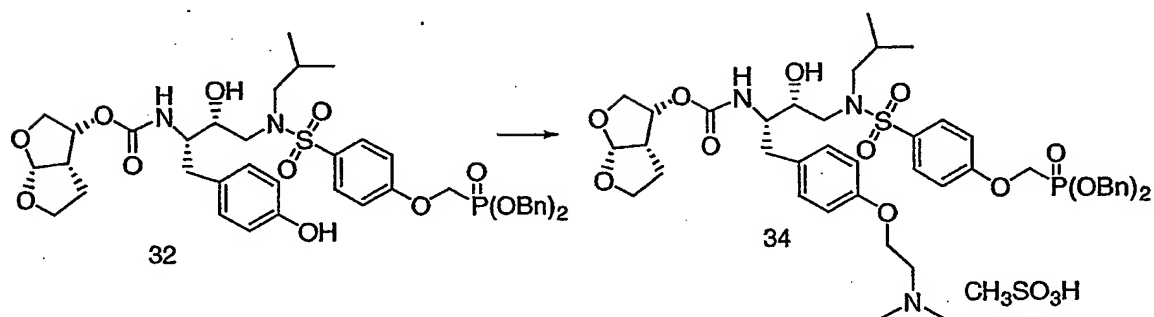
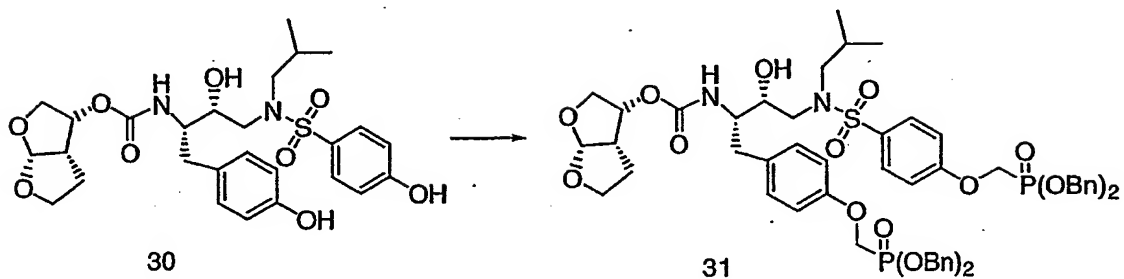
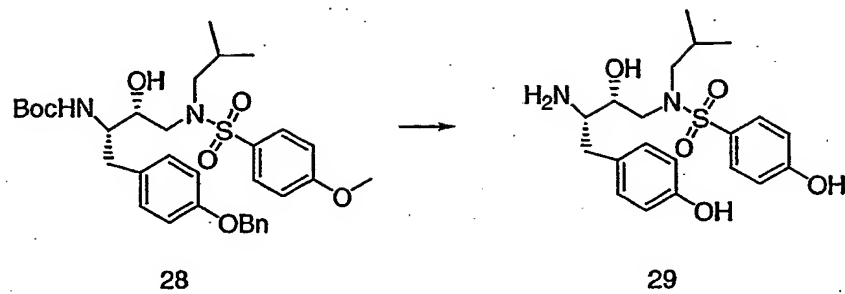
The following schemes are described in the Examples.





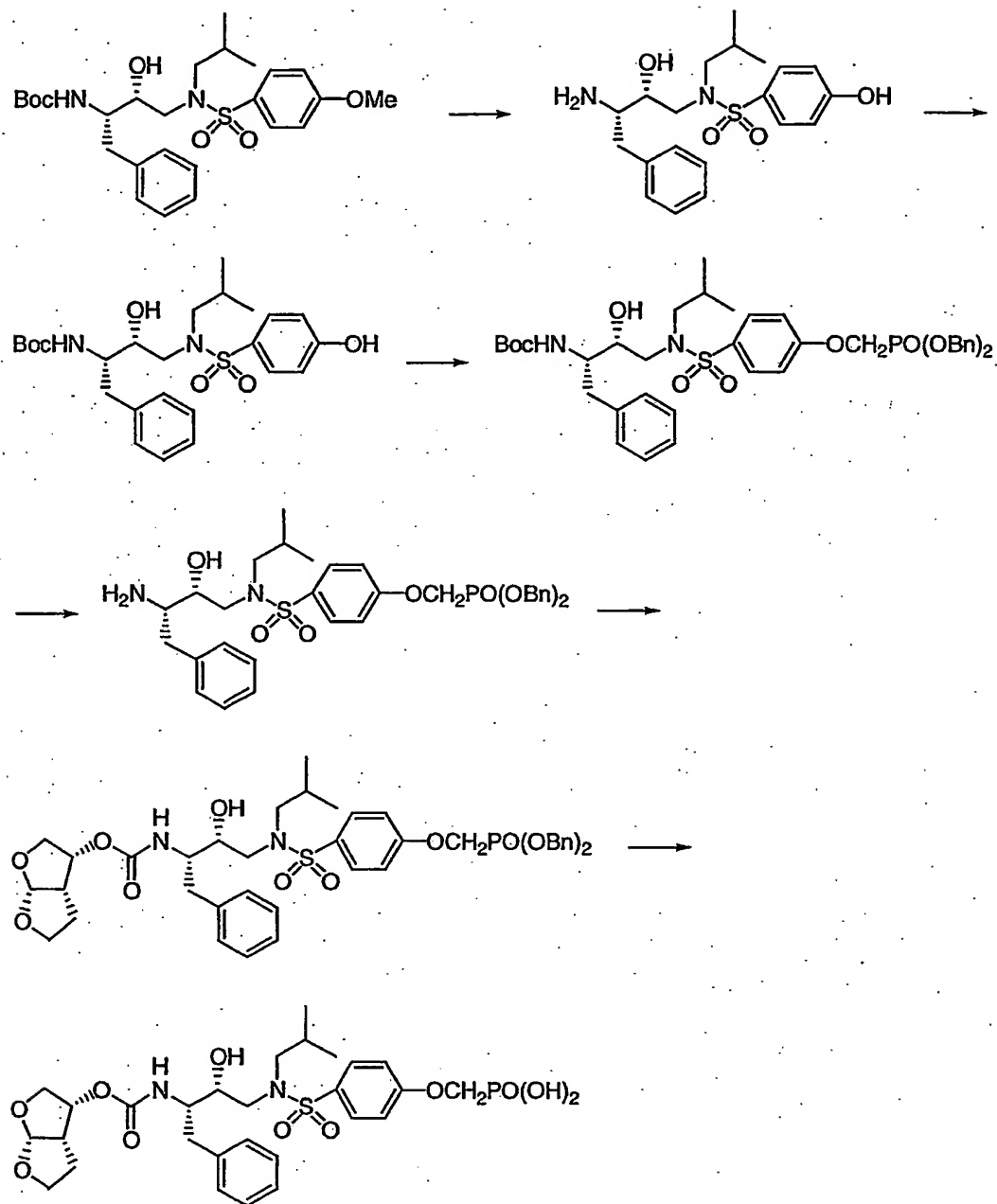




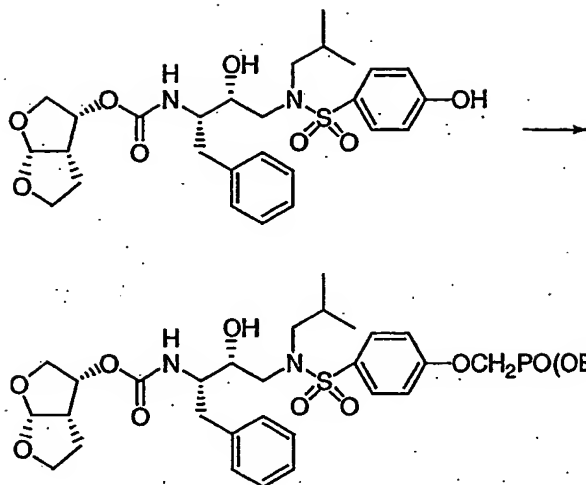


**Scheme Section E**

Schemes 1-3 are described in the examples.

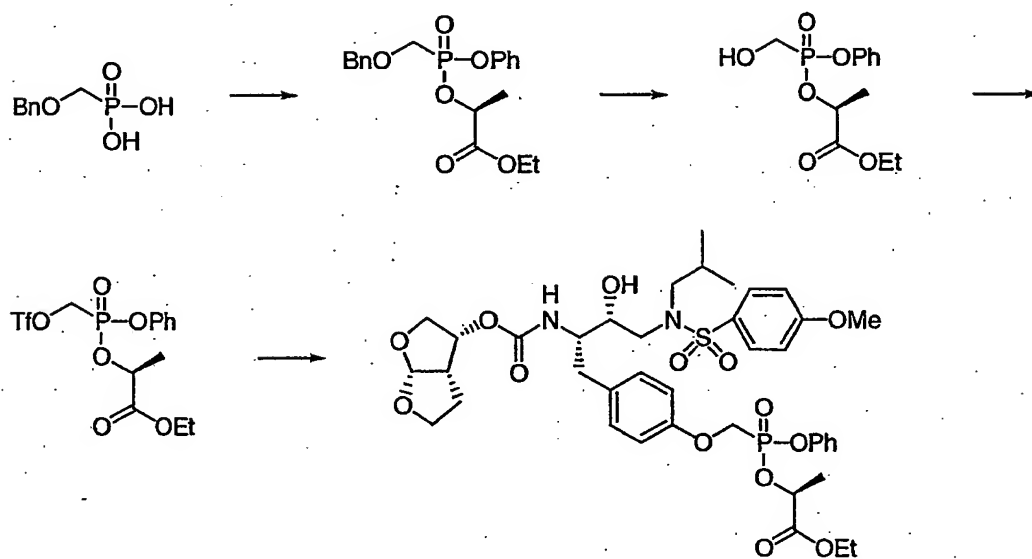
**Scheme 1**

Scheme 2



5

Scheme 3



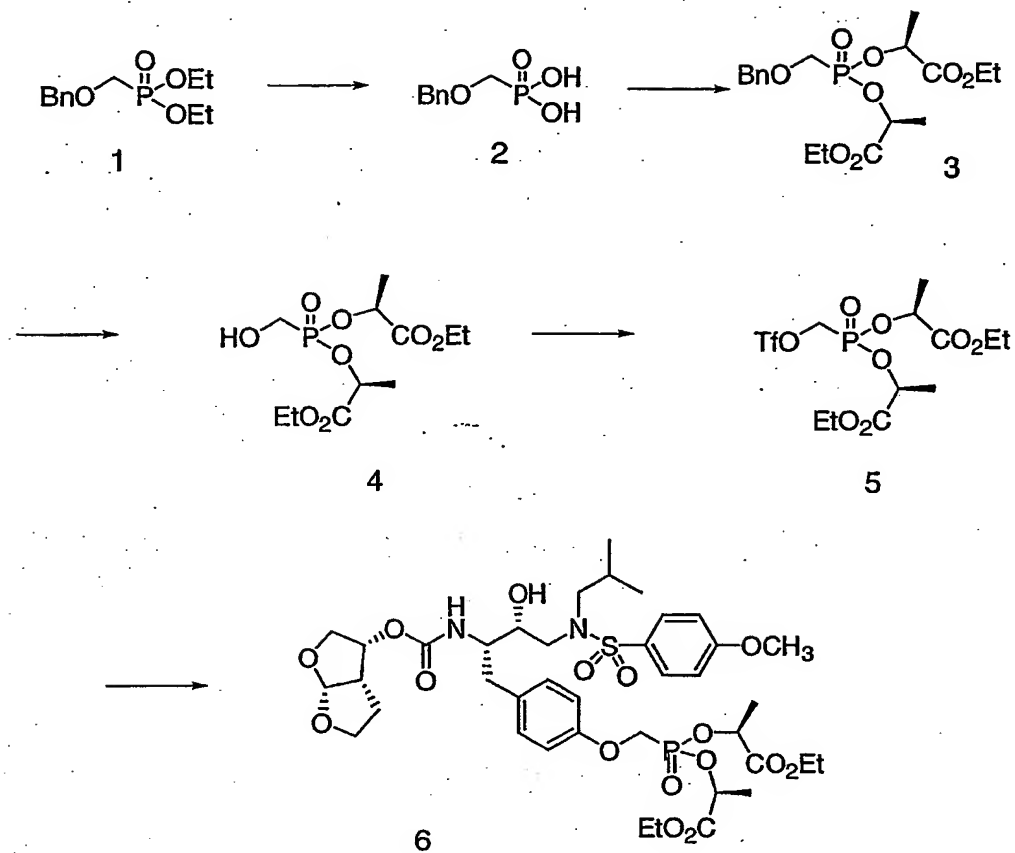


**Scheme Section F**

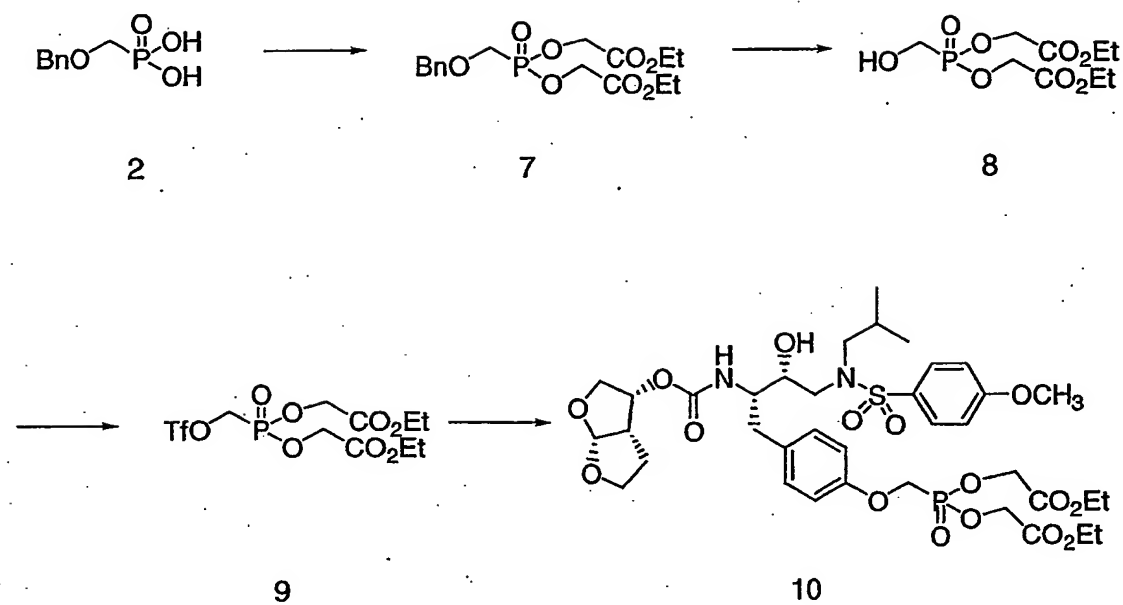
Schemes 1-5 are described in the examples.

**Scheme 1**

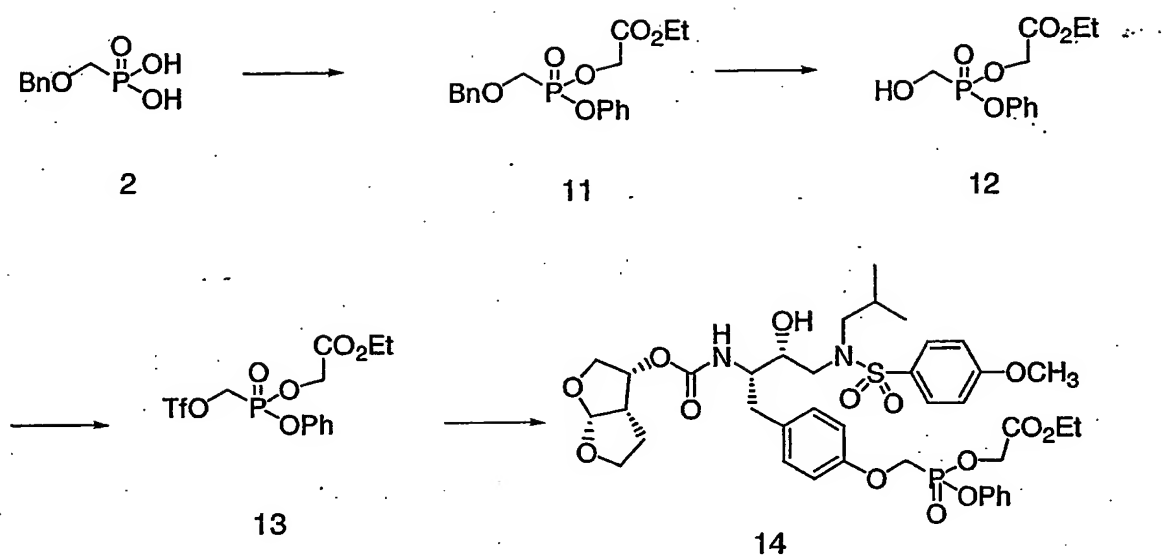
5



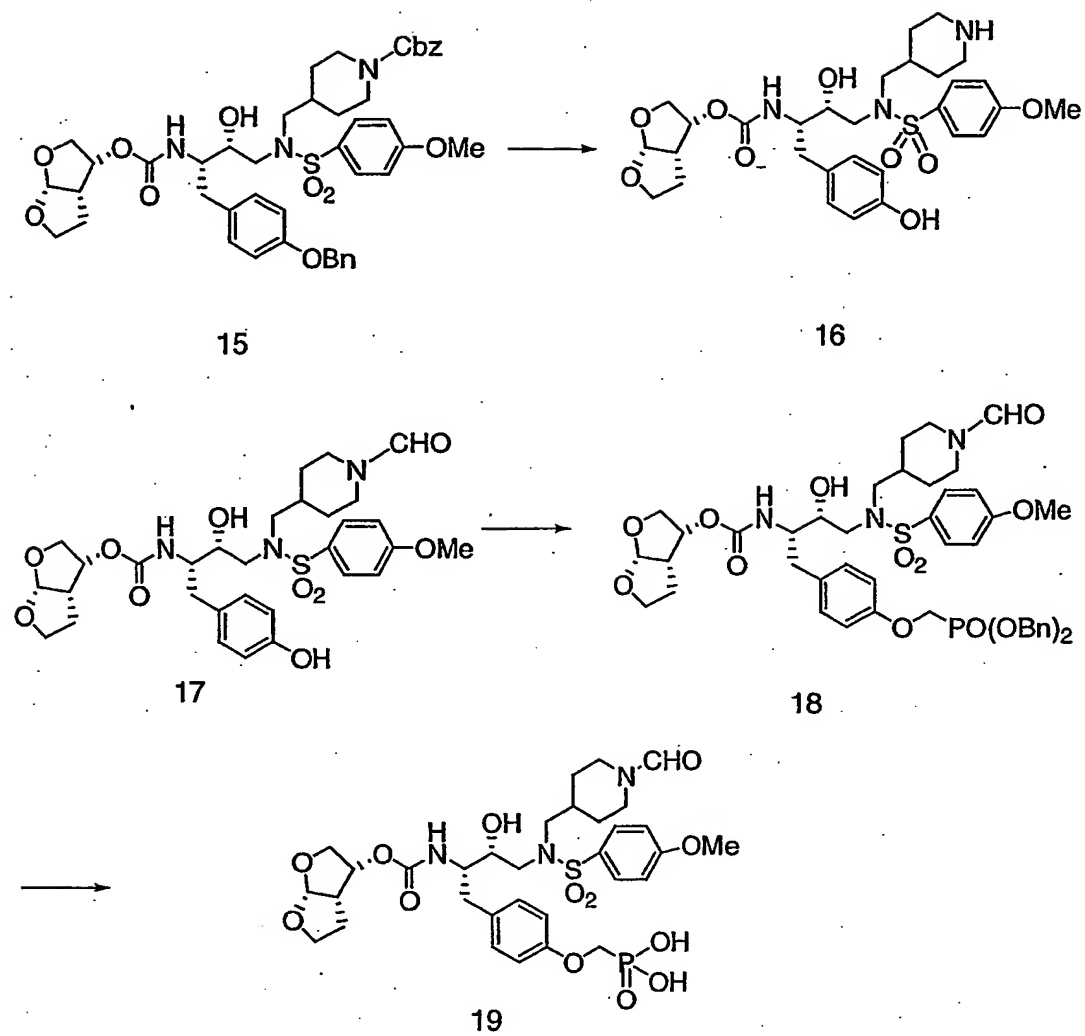
Scheme 2



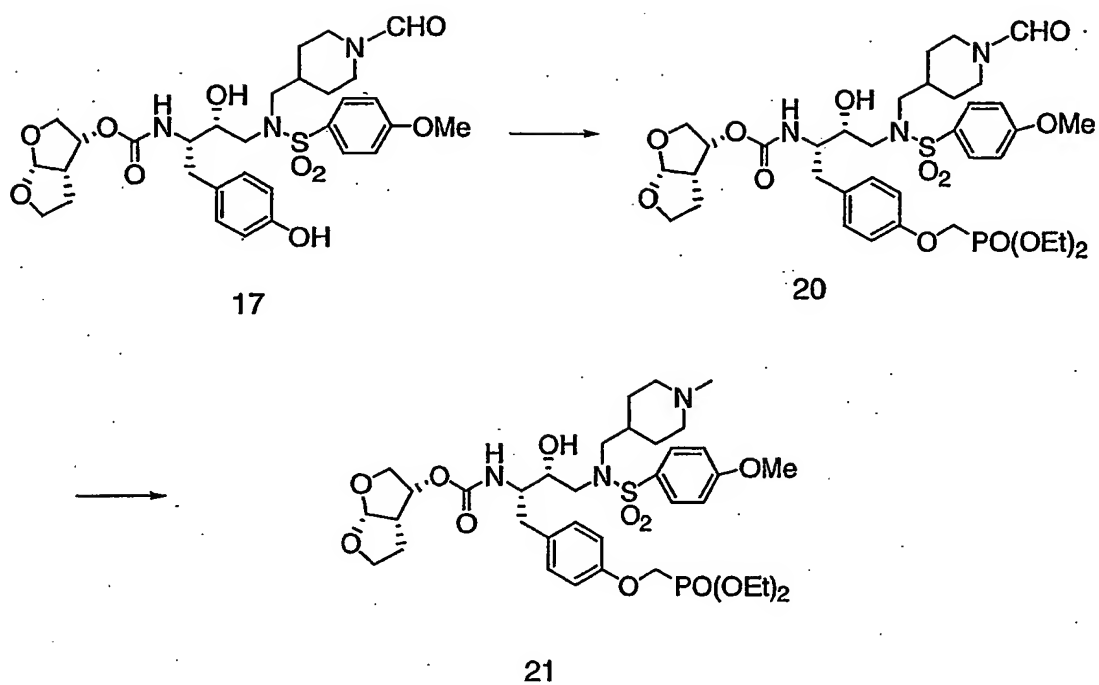
## Scheme 3



Scheme 4

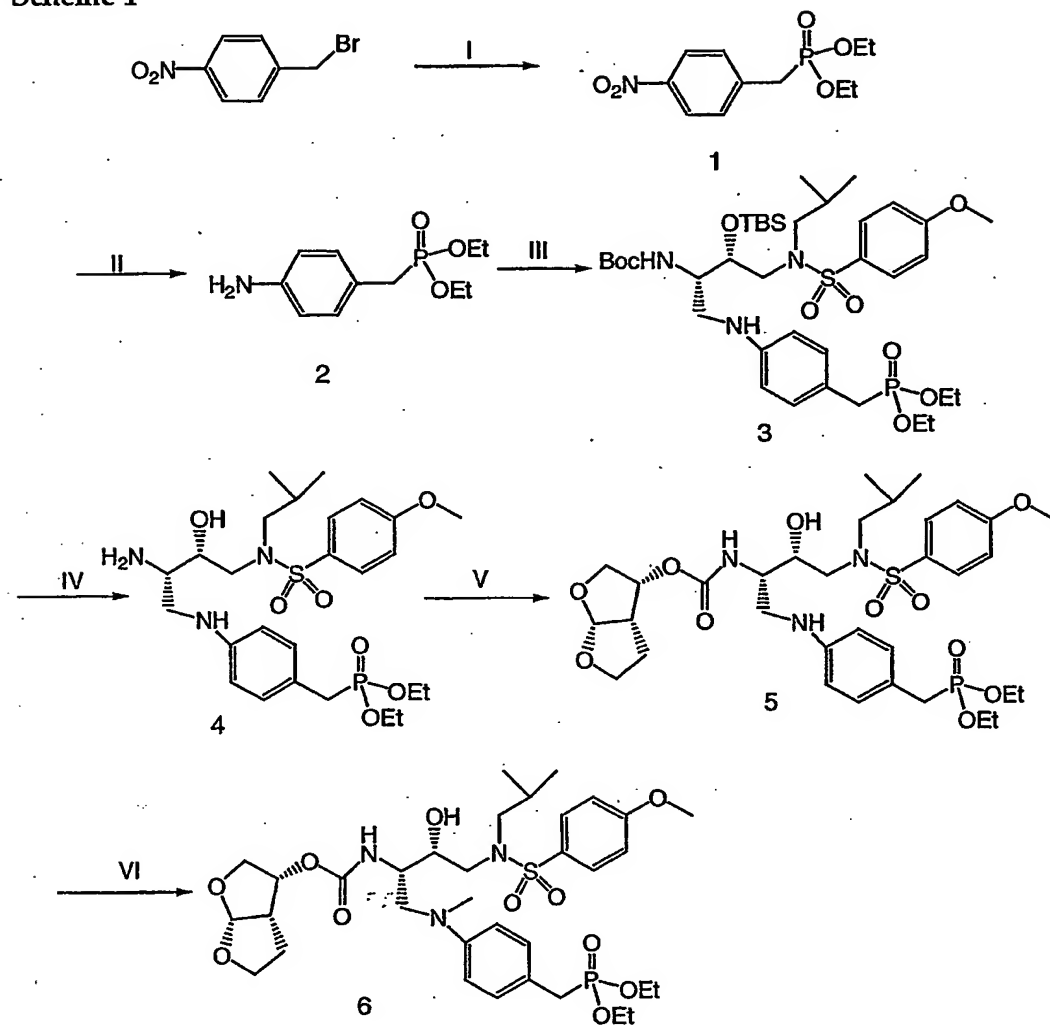


Scheme 5



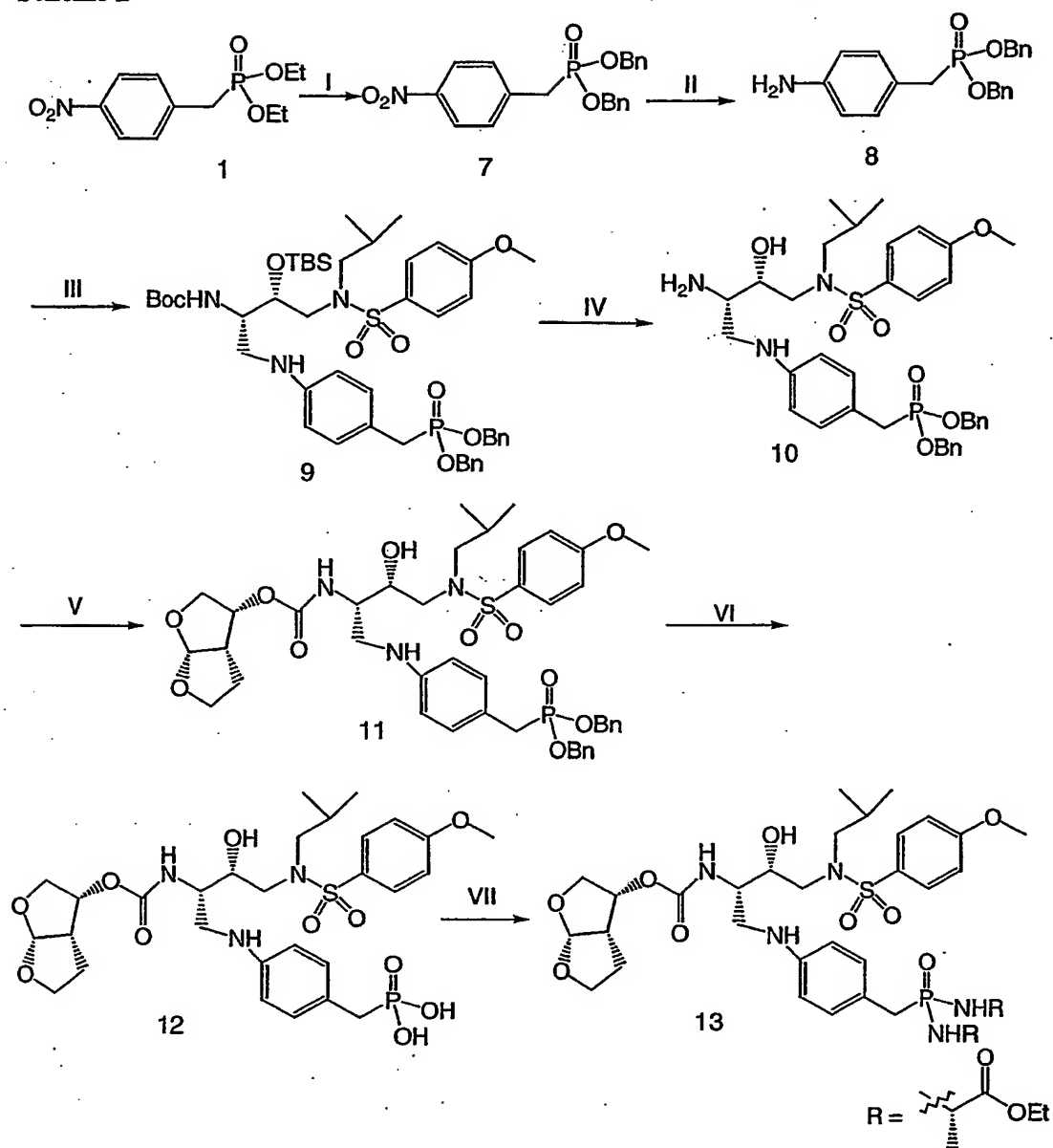
**Scheme Section G**

Schemes 1 to 9 are described in the examples.

**Scheme 1**

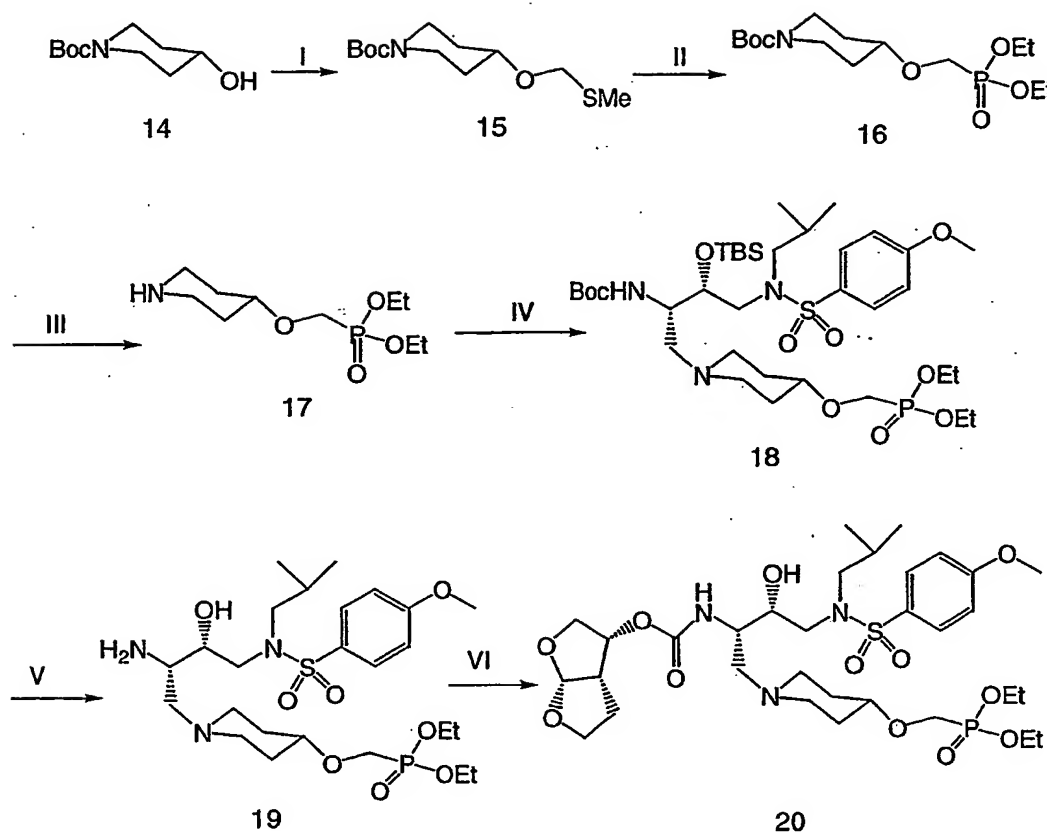
I.  $\text{P(OEt)}_3/120^\circ\text{C}$ ; II.  $\text{H}_2/10\%\text{Pd-C}$ ; III. See Scheme Section H, Scheme 13, Compound 48 /  $\text{NaBH}_3\text{CN}/\text{HOAc}/\text{MeOH}$ ; IV. a. TFA; b.  $n\text{-Bu}_4\text{NF}$ ; V. bisfuran carbonate/DMAP; VI.  $\text{HCHO}/\text{NaBH}_3\text{CN}/\text{HOAc}/\text{MeOH}$

Scheme 2



I. a. TMSBr; b.  $\text{SOCl}_2/60^\circ\text{C}$ ; c.  $\text{BnOH}/\text{Et}_3\text{N}$ ; II.  $\text{Zn}/\text{HOAc}$ ; III. See Scheme Section H, Scheme 13, Compound 48 /  $\text{NaBH}_3\text{CN}/\text{HOAc}/\text{MeOH}$ ; IV. a. TFA; b.  $n\text{-Bu}_4\text{NF}$ ; V. bisfurancarboxylate/DMAP; VI.  $\text{H}_2/10\%\text{Pd-C}$ ; VII.  $\text{RNH}_2/\text{PPh}_3/\text{aldrithiol}$

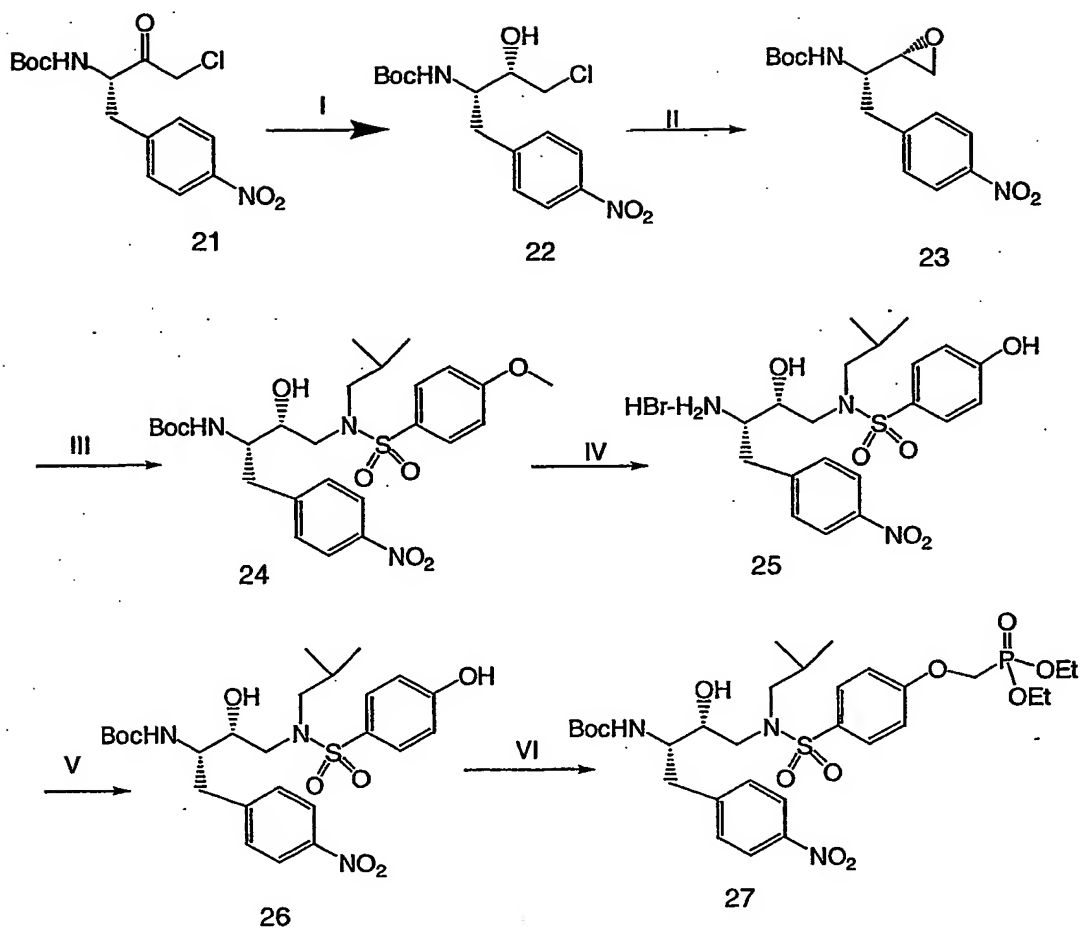
Scheme 3



I. a. NaH; b. MTMCl; II. a. SOCl<sub>2</sub>; b. P(OEt)<sub>3</sub>/120 °C; III. TFA; IV. See Scheme Section H, Scheme 13, Compound 48 / NaBH<sub>3</sub>CN/HOAc/MeOH; V. a. TFA; b. n-Bu<sub>4</sub>NF; VI. bisfurancarboxylate/DMAP

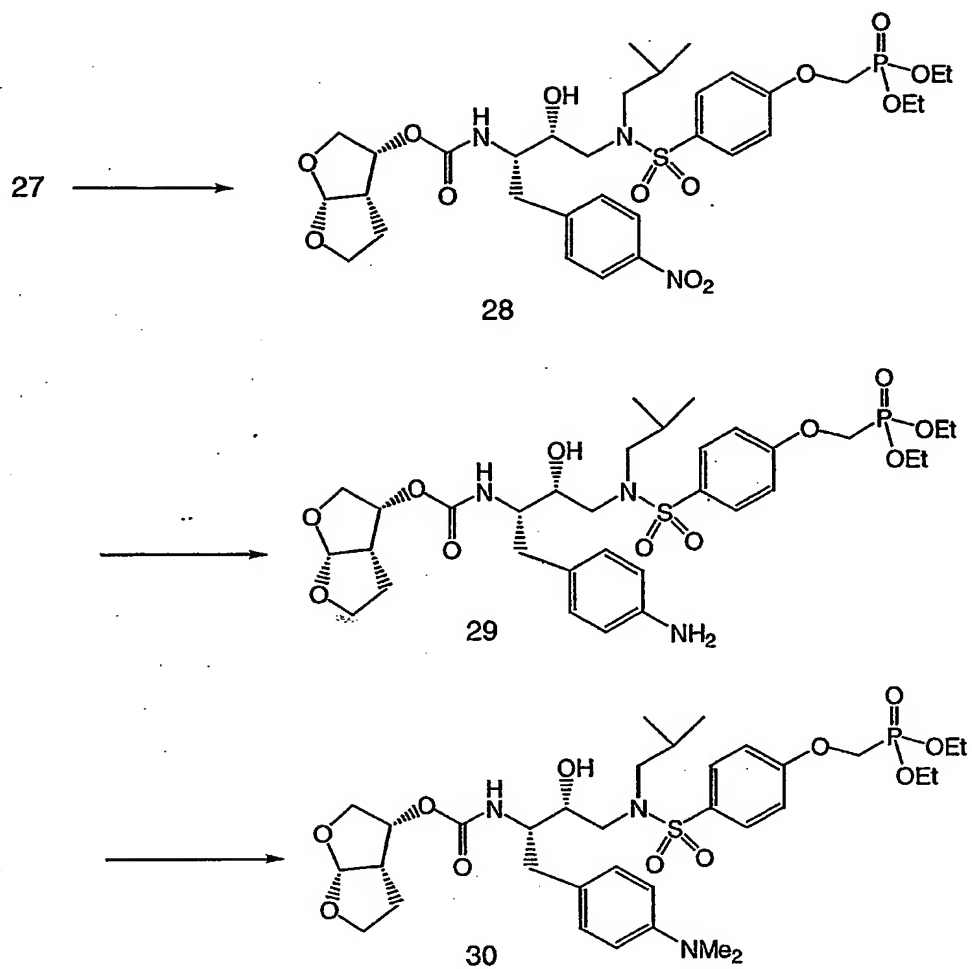


## Scheme 4



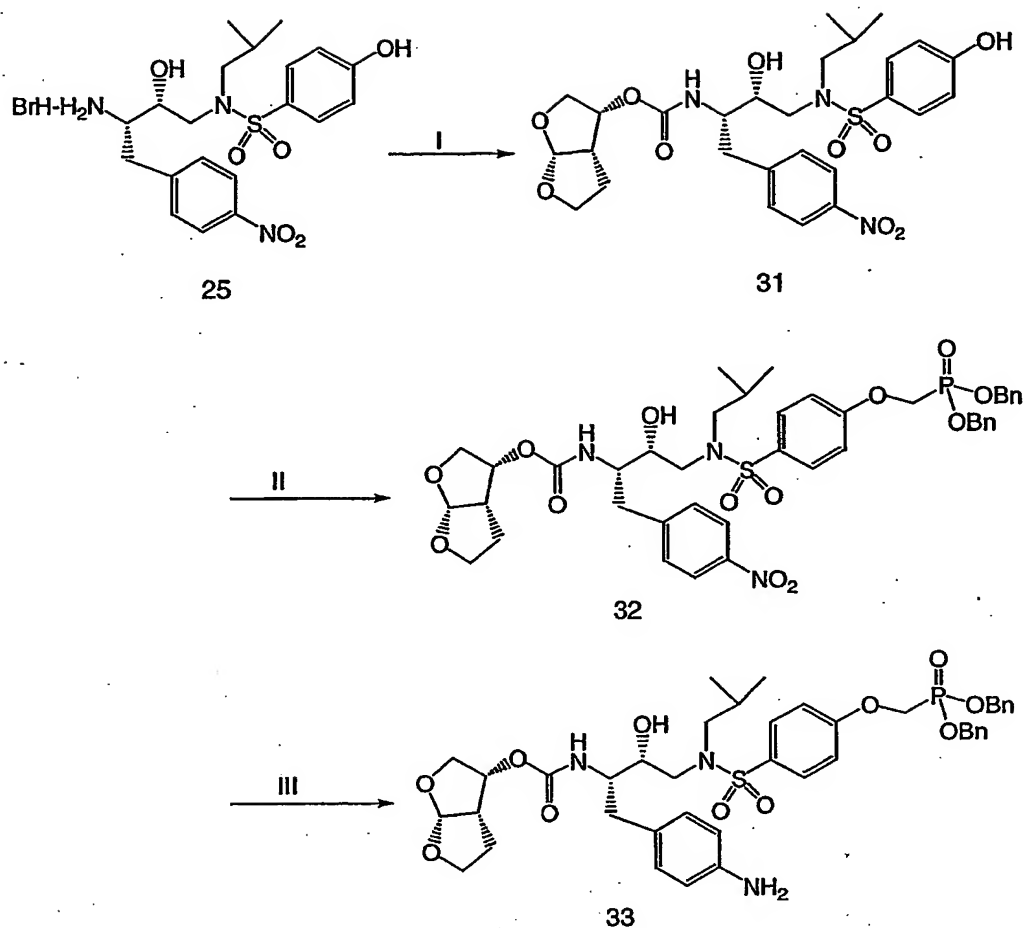
I.  $\text{NaBH}_4/\text{THF}/\text{H}_2\text{O}$ ; II.  $\text{KOH}/\text{EtOH}$ ; III. a. isobutylamine/isopropanol/80 °C; b. 4-methoxybenzenesulfonyl chloride/ $\text{Et}_3\text{N}$ ; IV.  $\text{BBr}_3/\text{CH}_2\text{Cl}_2$ ; V.  $\text{Boc}_2\text{O}/\text{NaHCO}_3$ ; VI.  $\text{Ti}(\text{OCH}_2)_2\text{PO}(\text{OEt})_2/\text{Cs}_2\text{CO}_3$

## Scheme 5



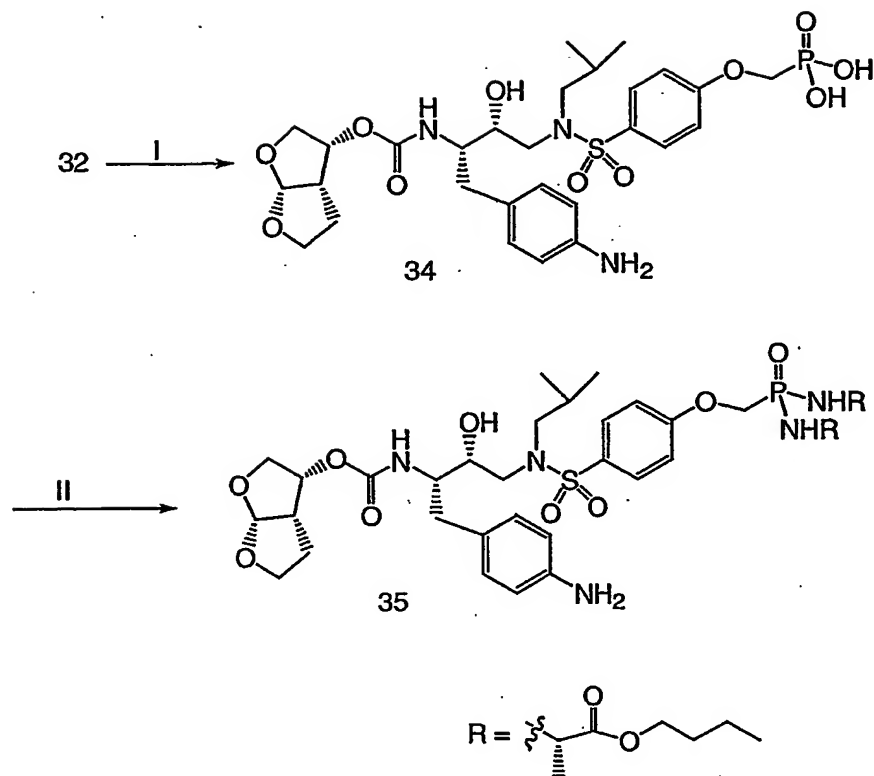
I. TFA/CH<sub>2</sub>Cl<sub>2</sub>; b. bisfurancarboxylate/DMAP ; II. H<sub>2</sub>/10% Pd-C/EtOH;  
III. HCHO/NaBH<sub>3</sub>CN/HOAc/MeOH

## Scheme 6



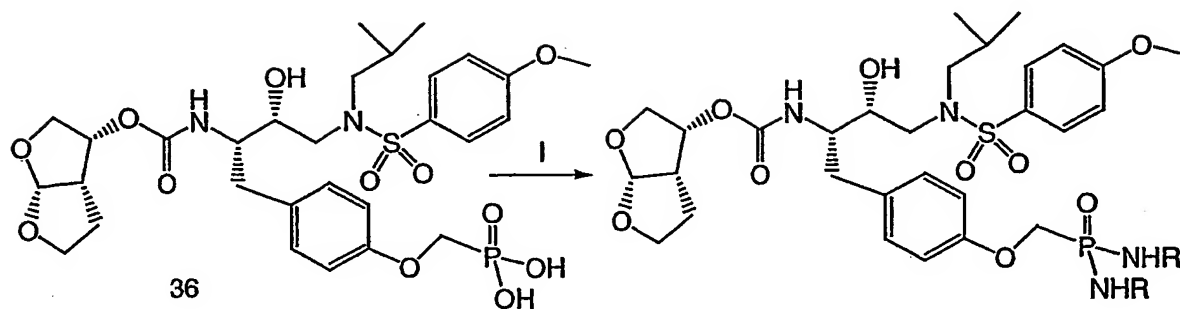
I. a.  $\text{TMSCl}/\text{Et}_3\text{N}$ ; b. bisfuran carbonate/ $\text{DMAP}$ ; c.  $n\text{-Bu}_4\text{NF}/\text{HOAc}$ ; II.  $\text{Ti}(\text{OCH}_2\text{P}(\text{OBn})_2)_2/\text{Cs}_2\text{CO}_3$ ; III.  $\text{Zn}/\text{HOAc}$

Scheme 7

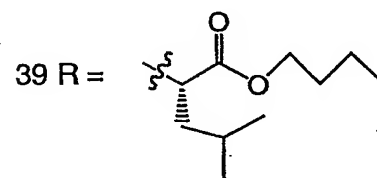
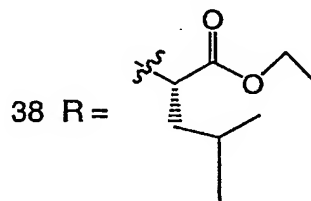
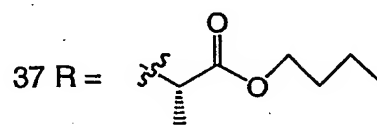


I. H<sub>2</sub>/10% Pd-C; II. RNH<sub>2</sub>/PPh<sub>3</sub>/Aldrithiol/diisopropylethylamine/pyridine

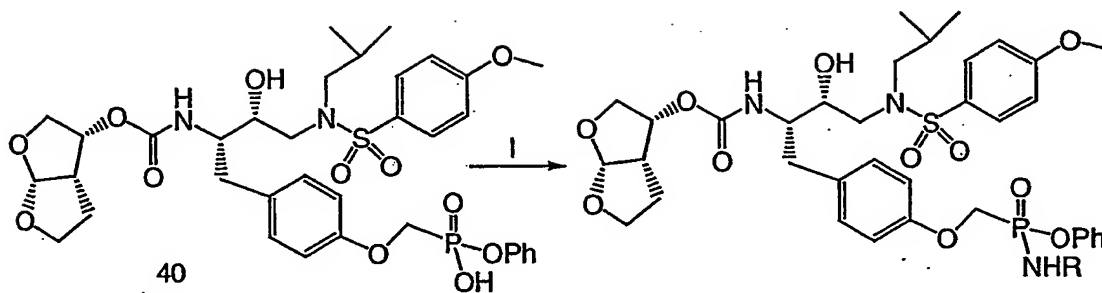
Scheme 8



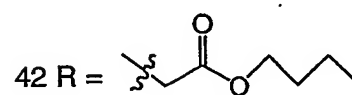
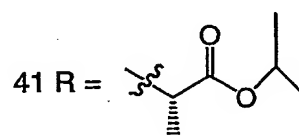
I.  $\text{RNH}_2/\text{PPh}_3/\text{Aldrithiol}/\text{diisopropylethylamine}/\text{pyridine}$



Scheme 9

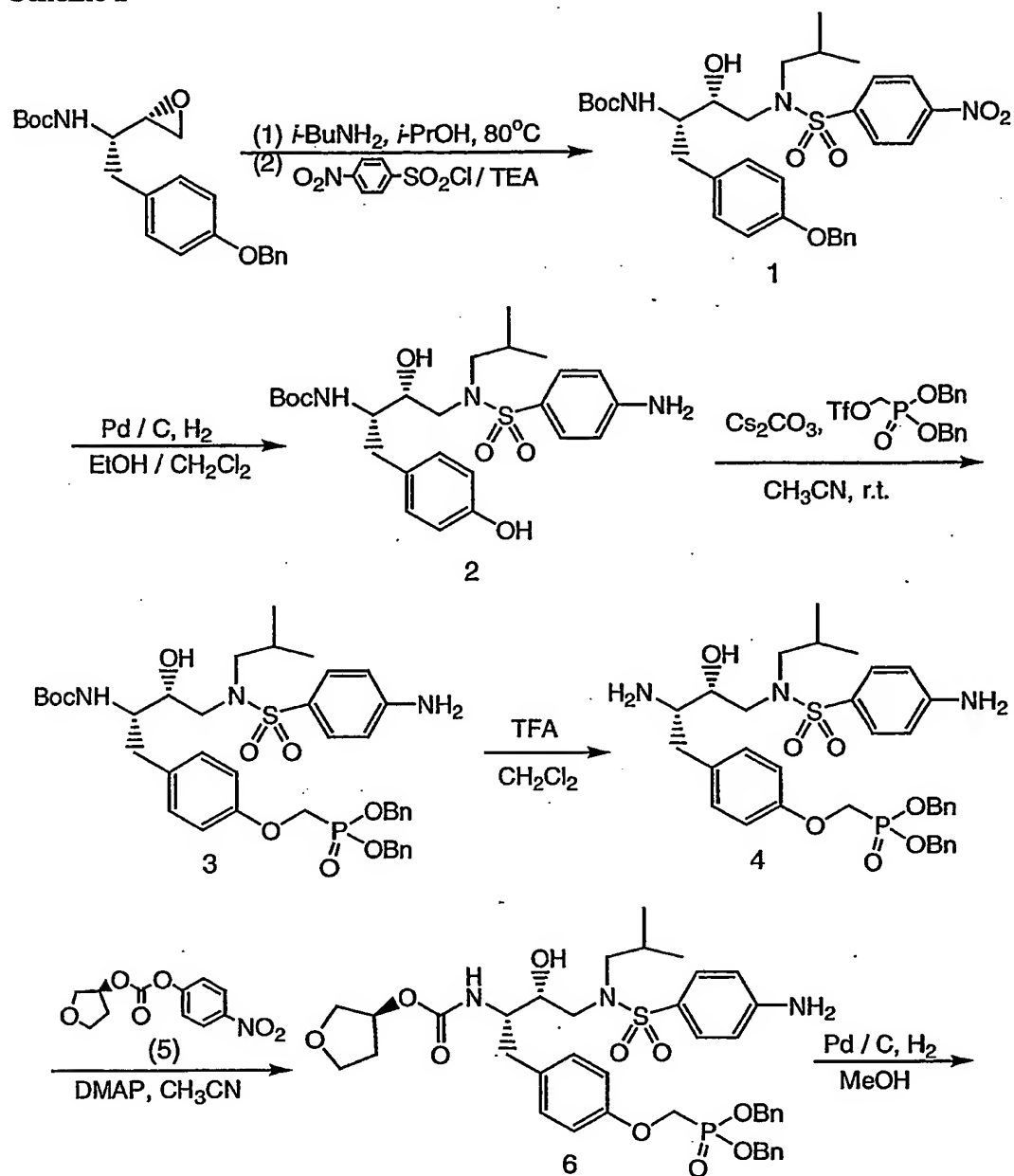


I.  $\text{RNH}_2/\text{PPh}_3/\text{Aldrithiol}/\text{diisopropylethylamine}/\text{pyridine}$



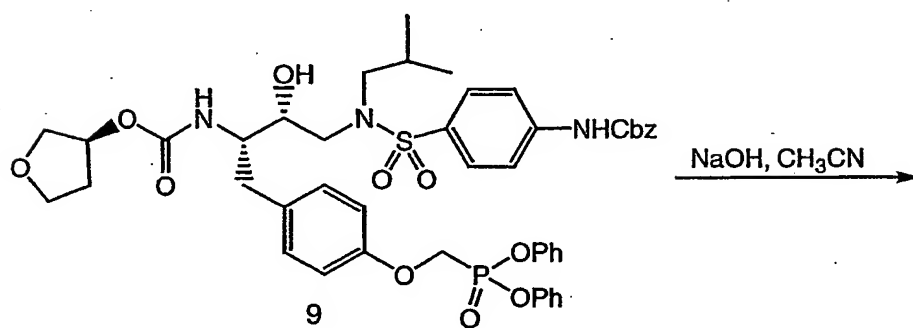
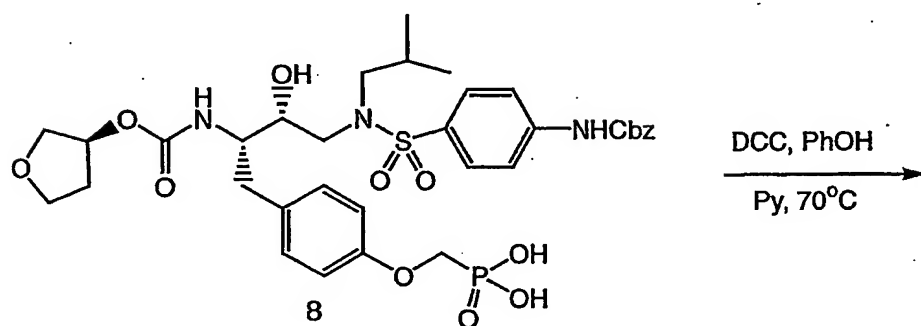
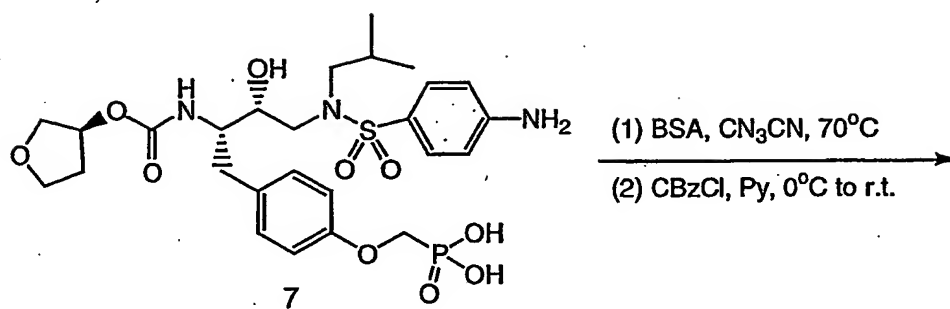
**Scheme Section H**

Schemes 1-14 are described in the examples.

**Scheme 1**

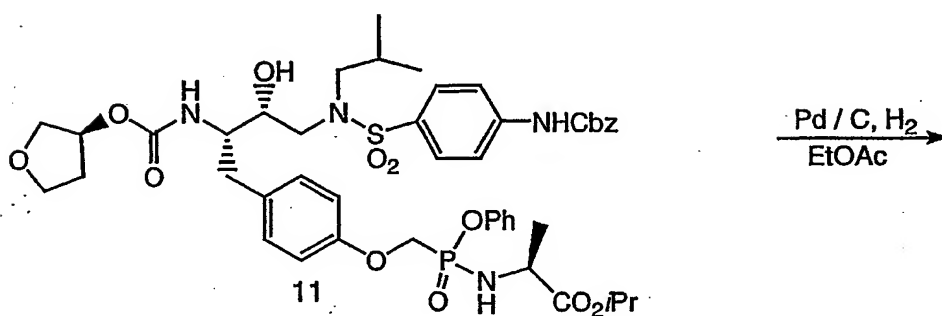
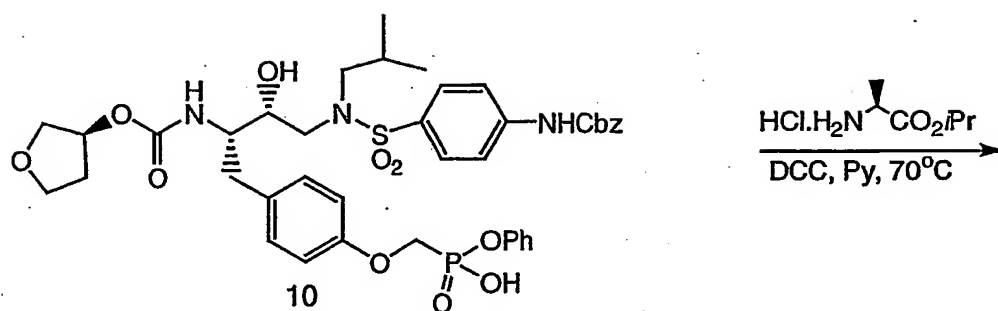
5

Scheme 2.





## Scheme 3

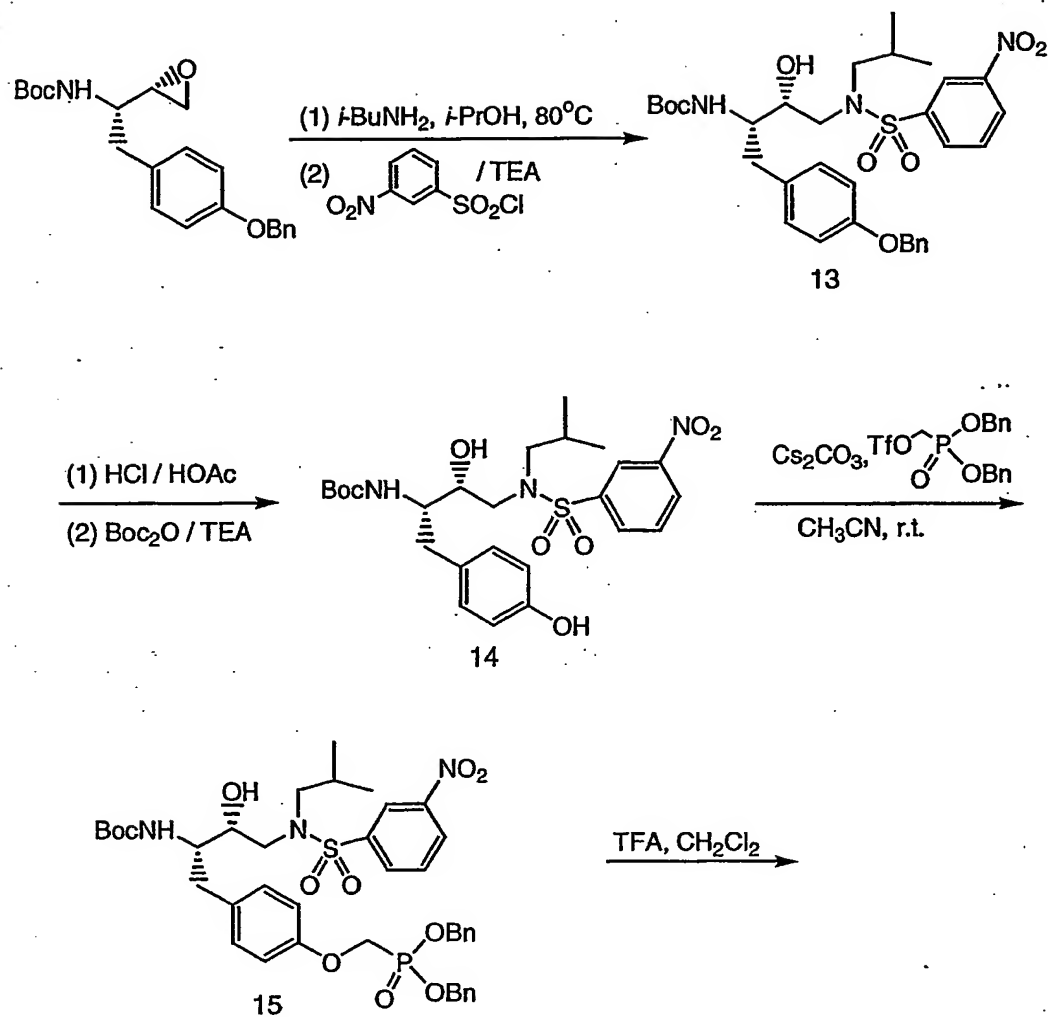


12a, GS 108577 (isomer A / B = 1 : 1)

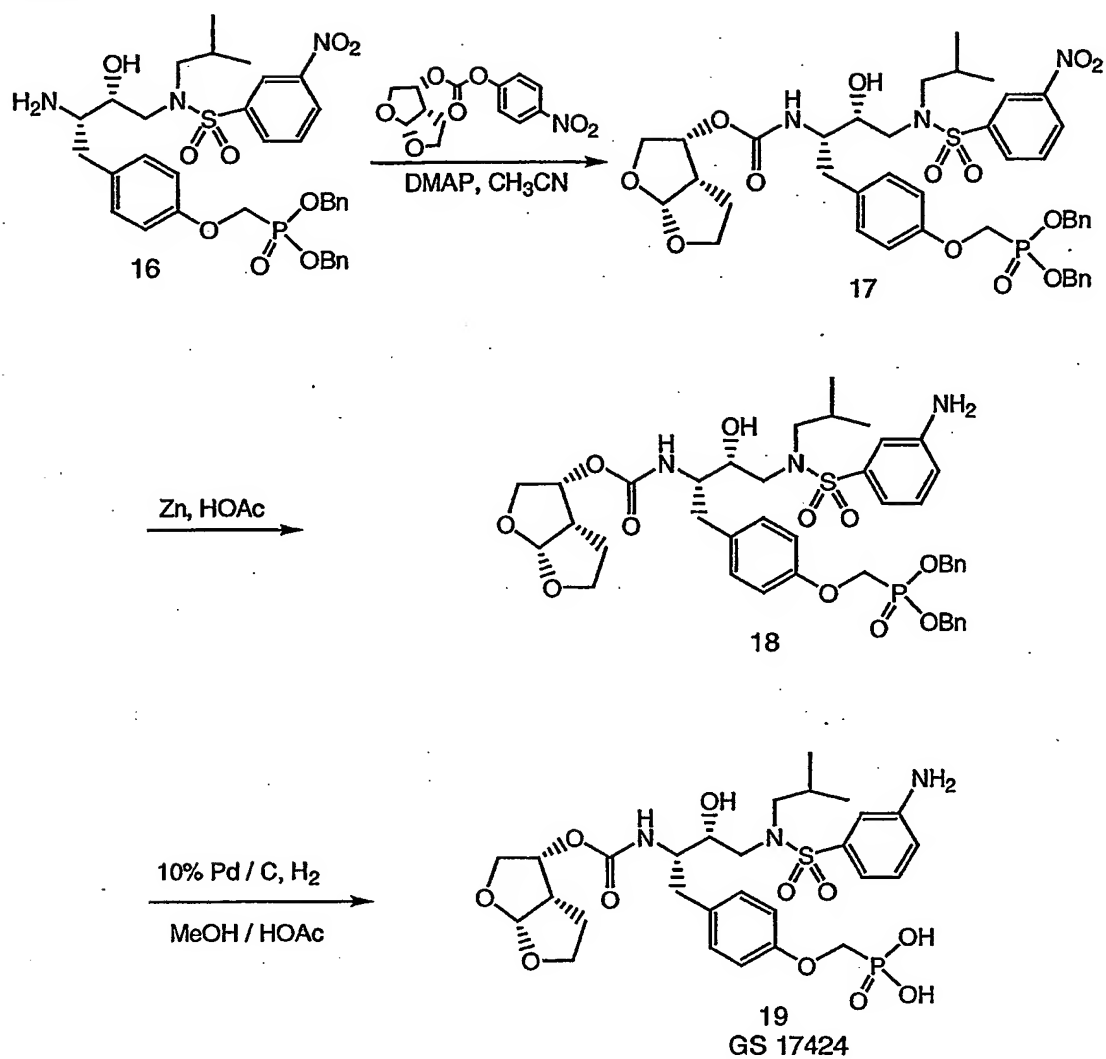
12b, GS 108578 (isomer A)

12c, GS 108579 (isomer B)

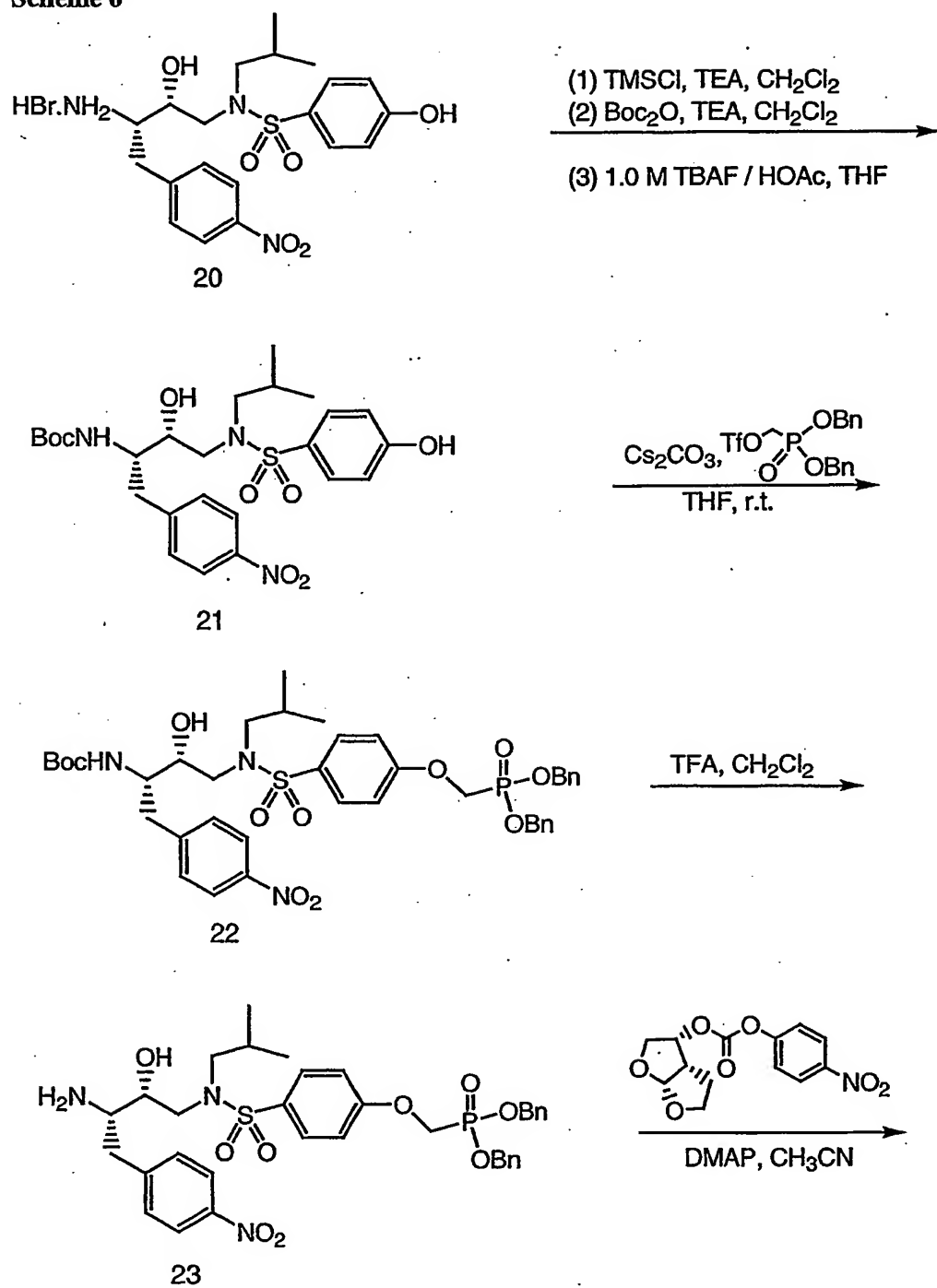
## Scheme 4



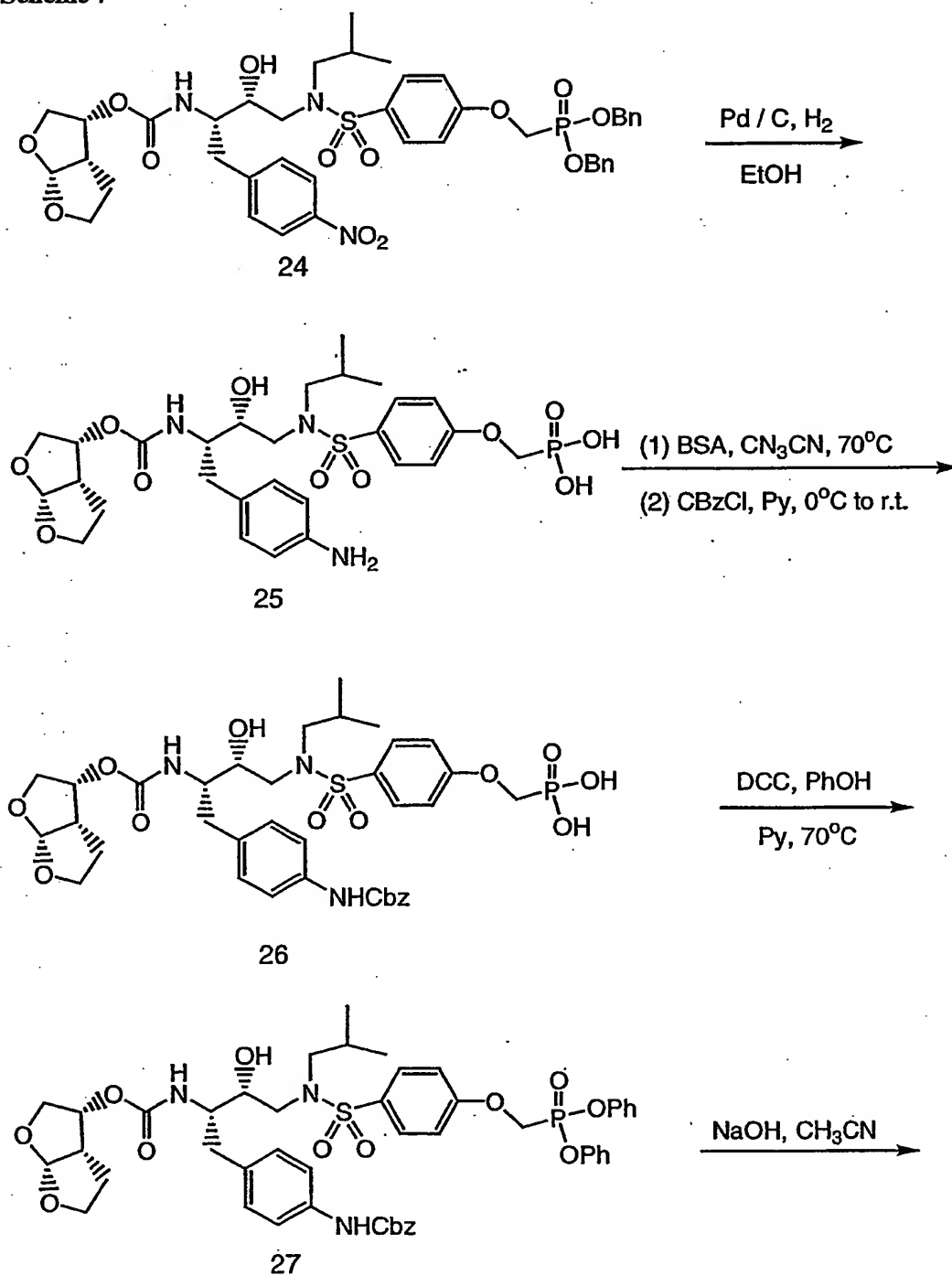
## Scheme 5



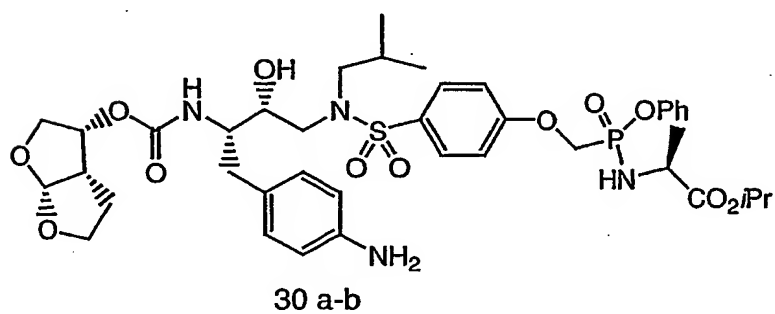
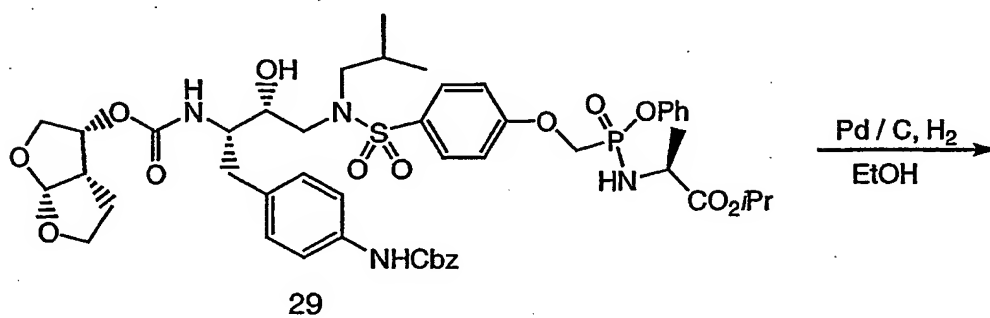
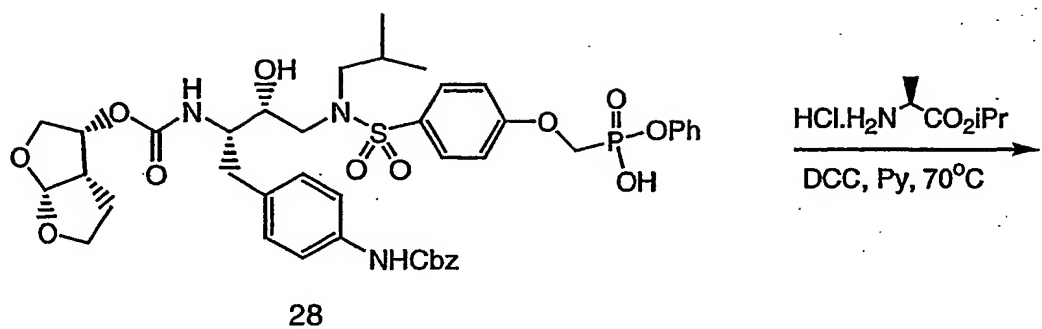
## Scheme 6



## Scheme 7

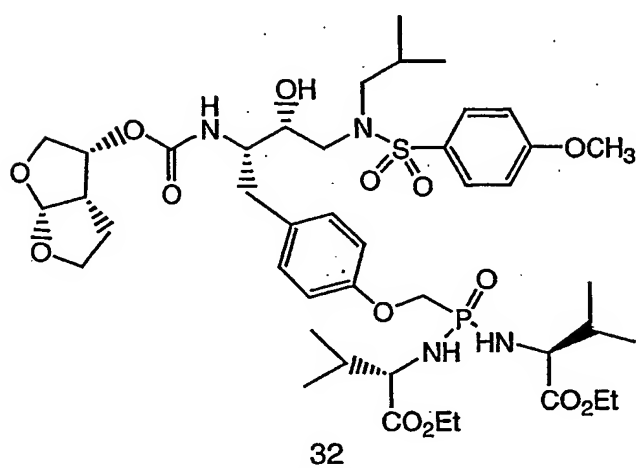
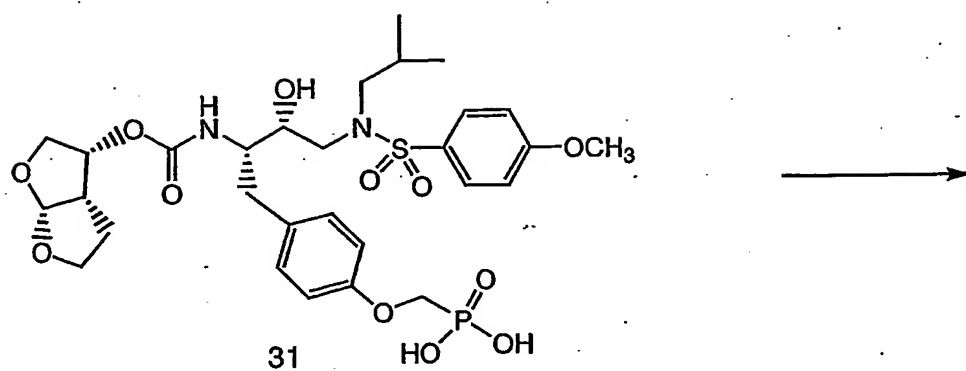


Scheme 8



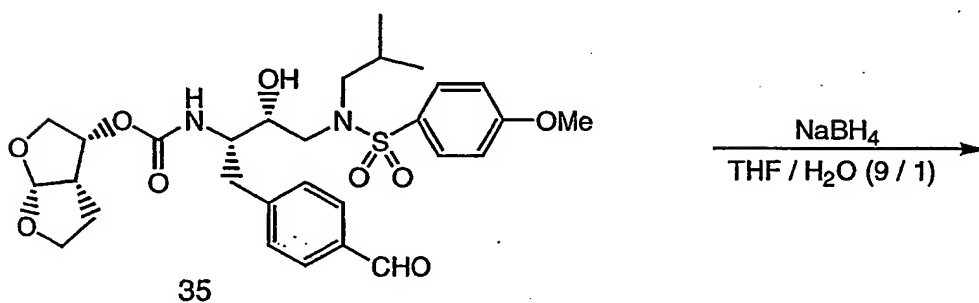
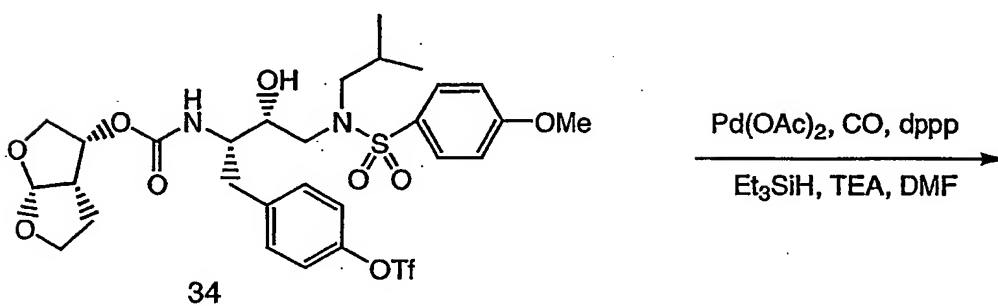
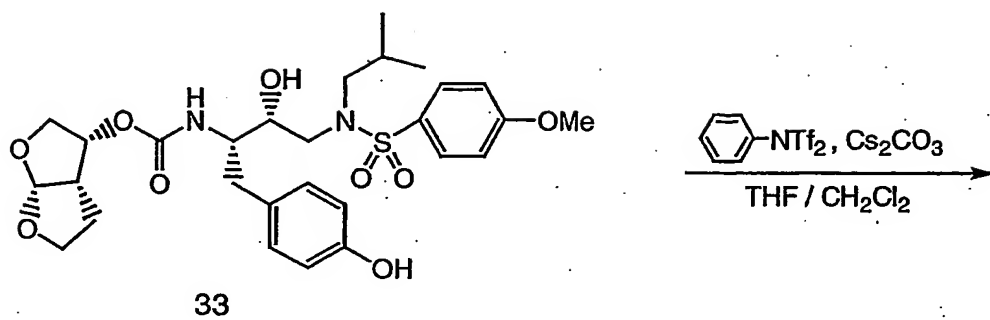
30a R = H, GS 77369  
 30b R = Et, GS 77425

Scheme 9



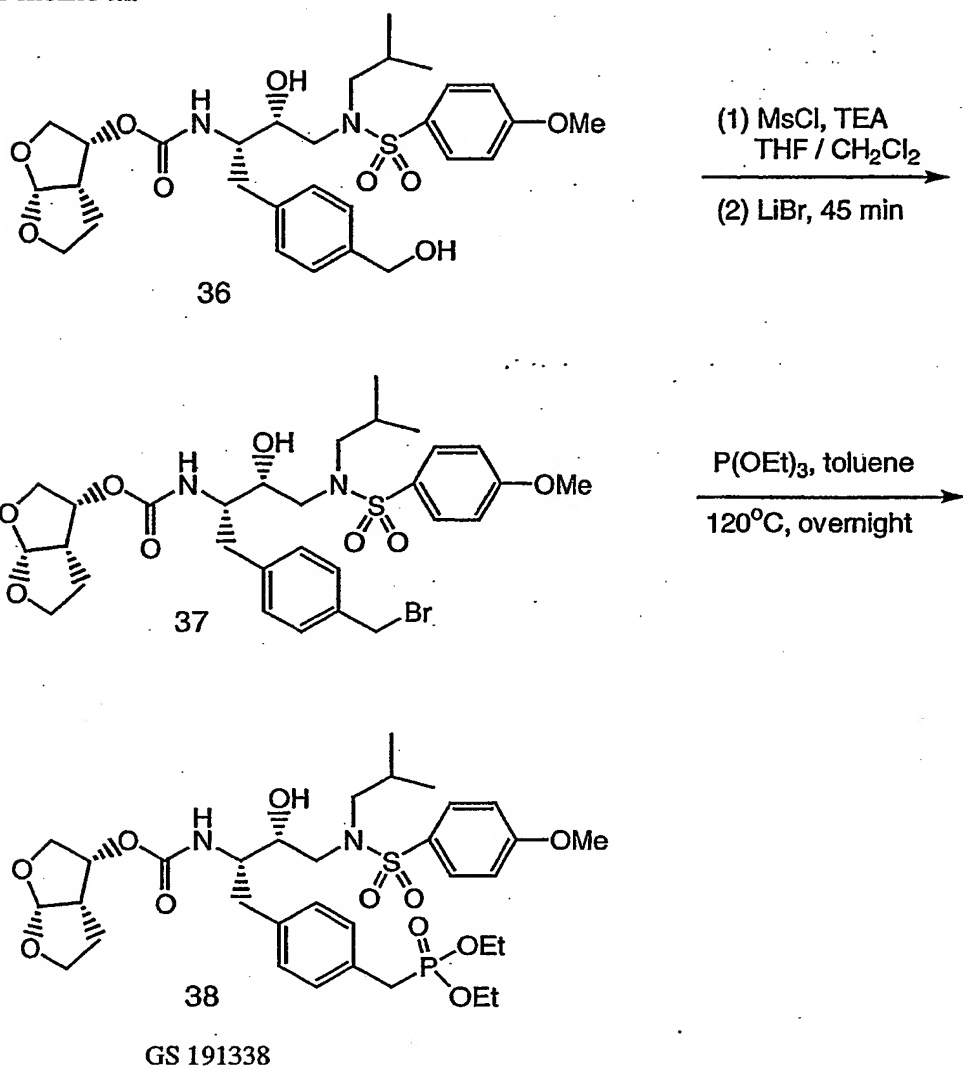
GS 17389

Scheme 10

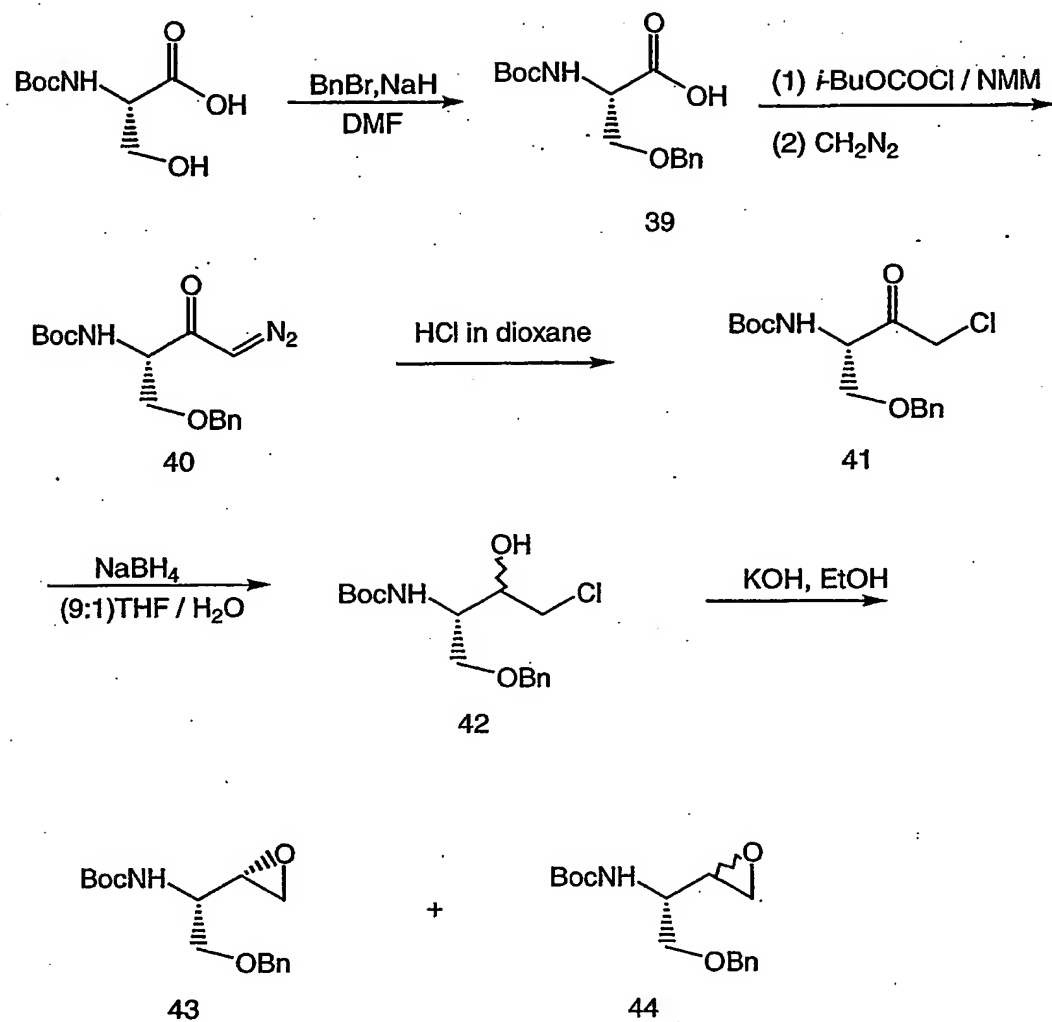




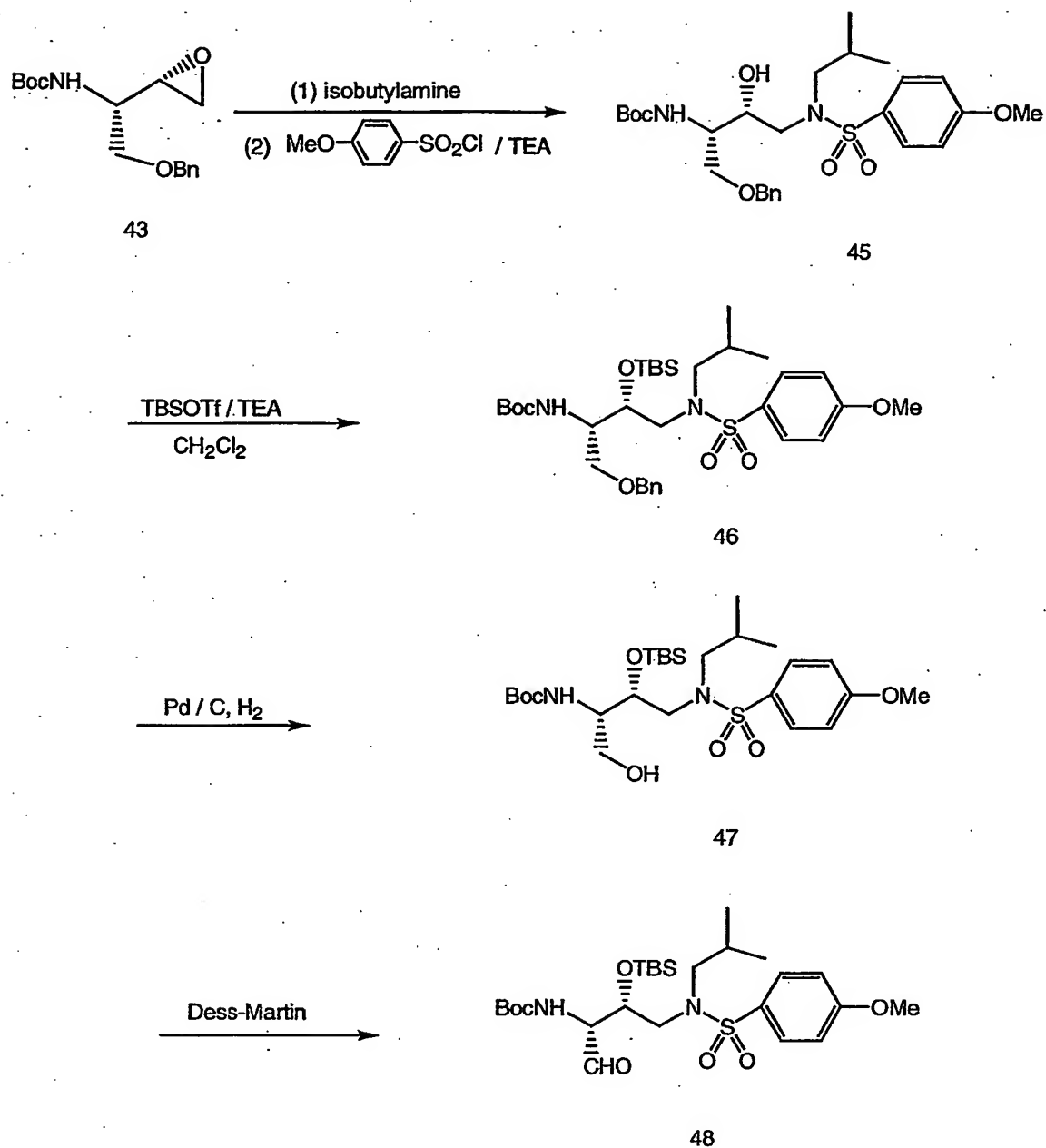
Scheme 11



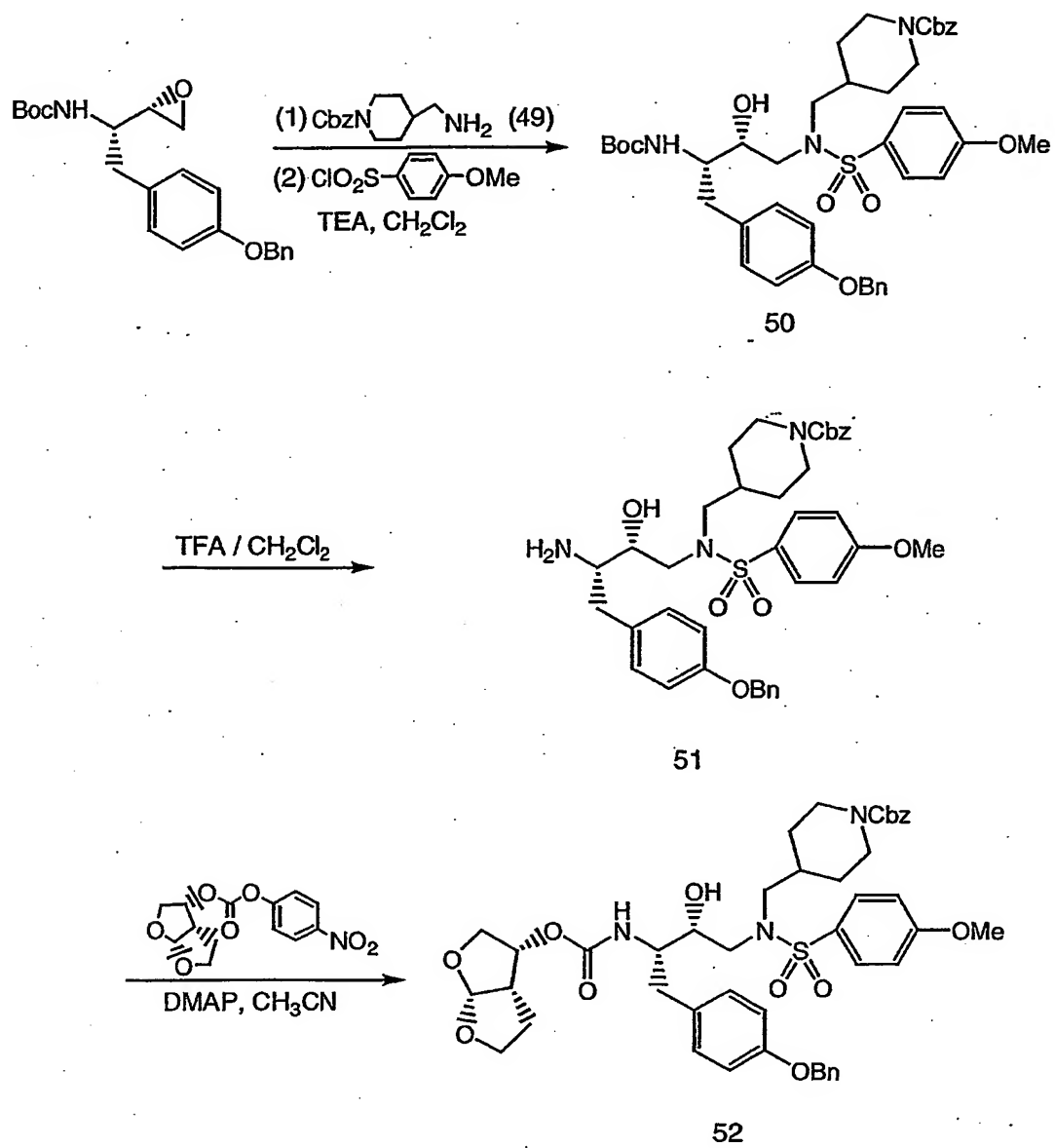
## Scheme 12



## Scheme 13

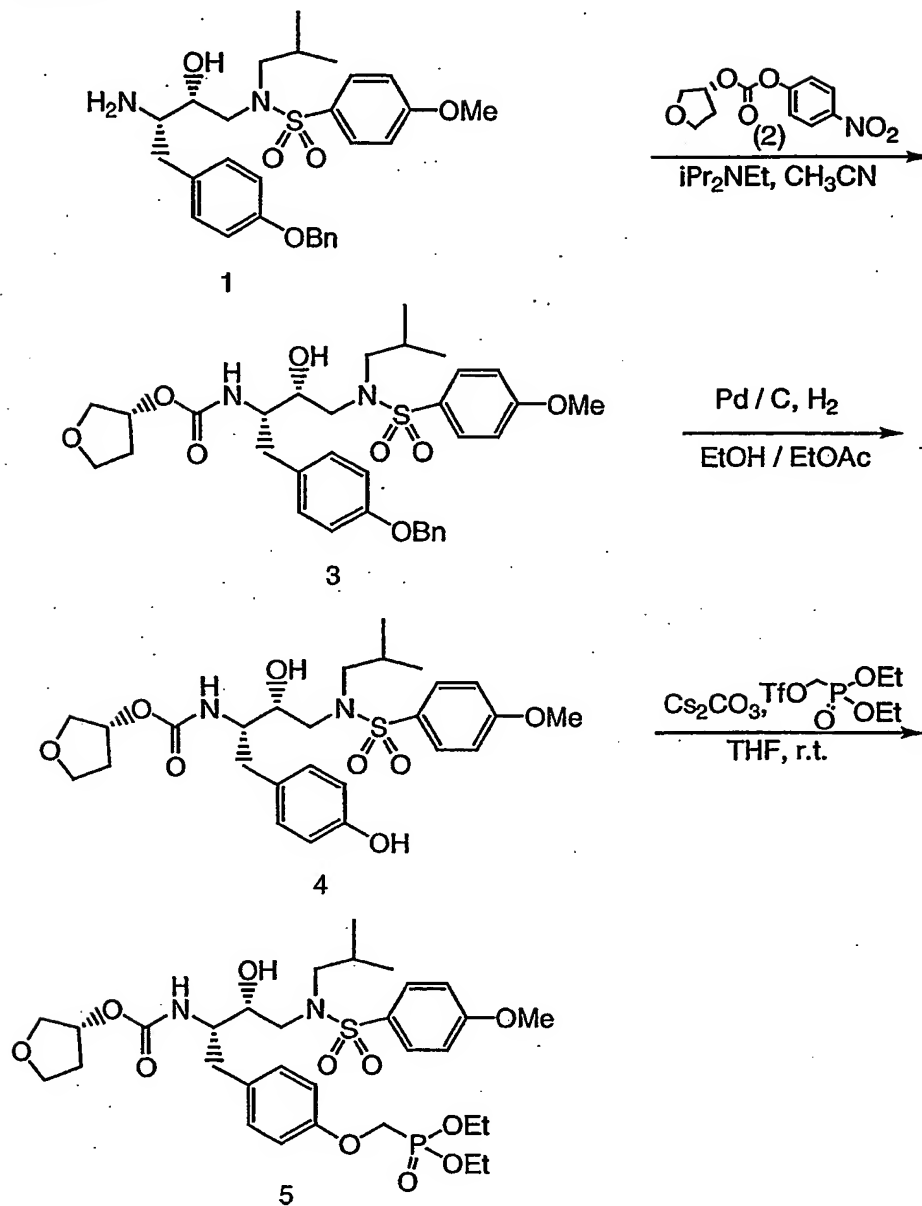


## Scheme 14



**Scheme Section I**

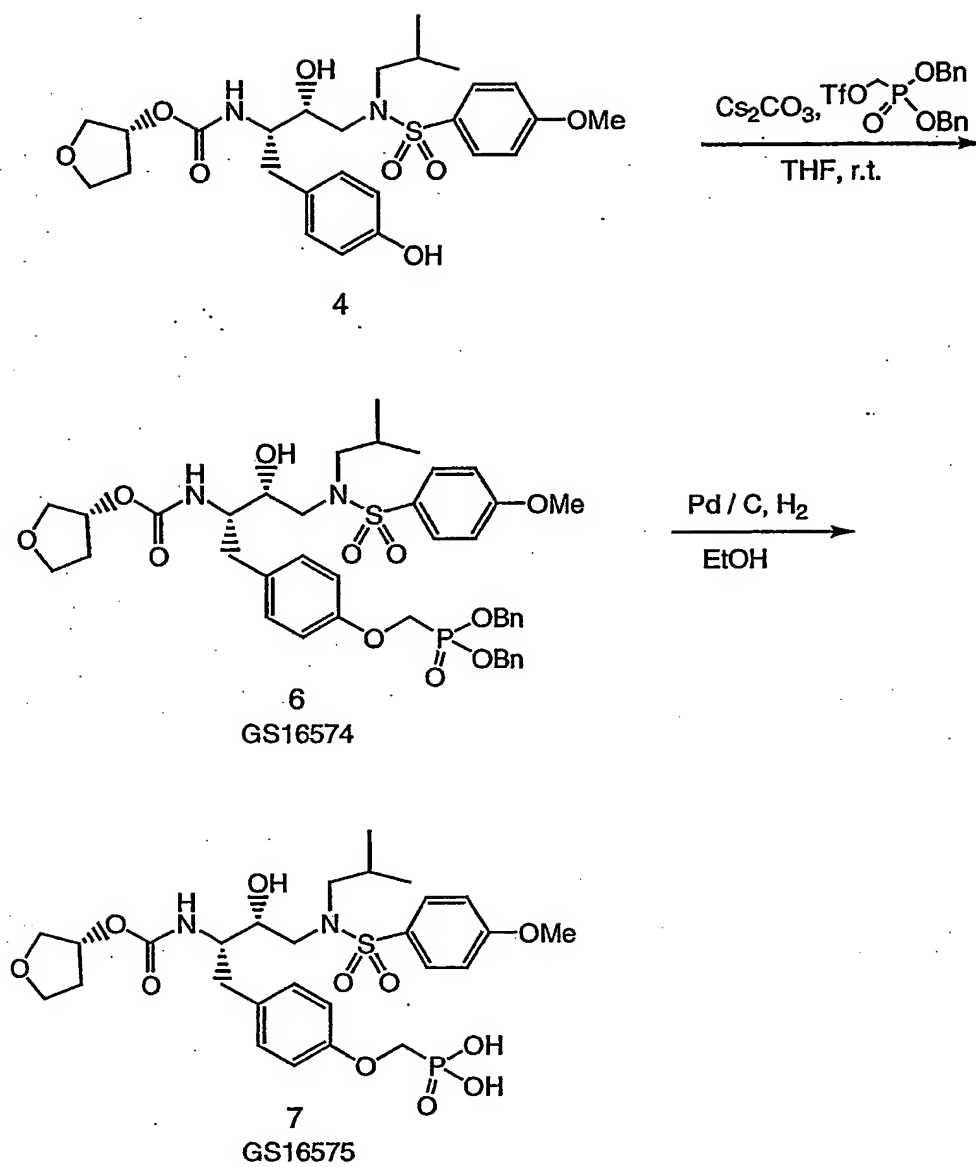
Schemes 1 to 3 are described in the examples.

**Scheme 1**

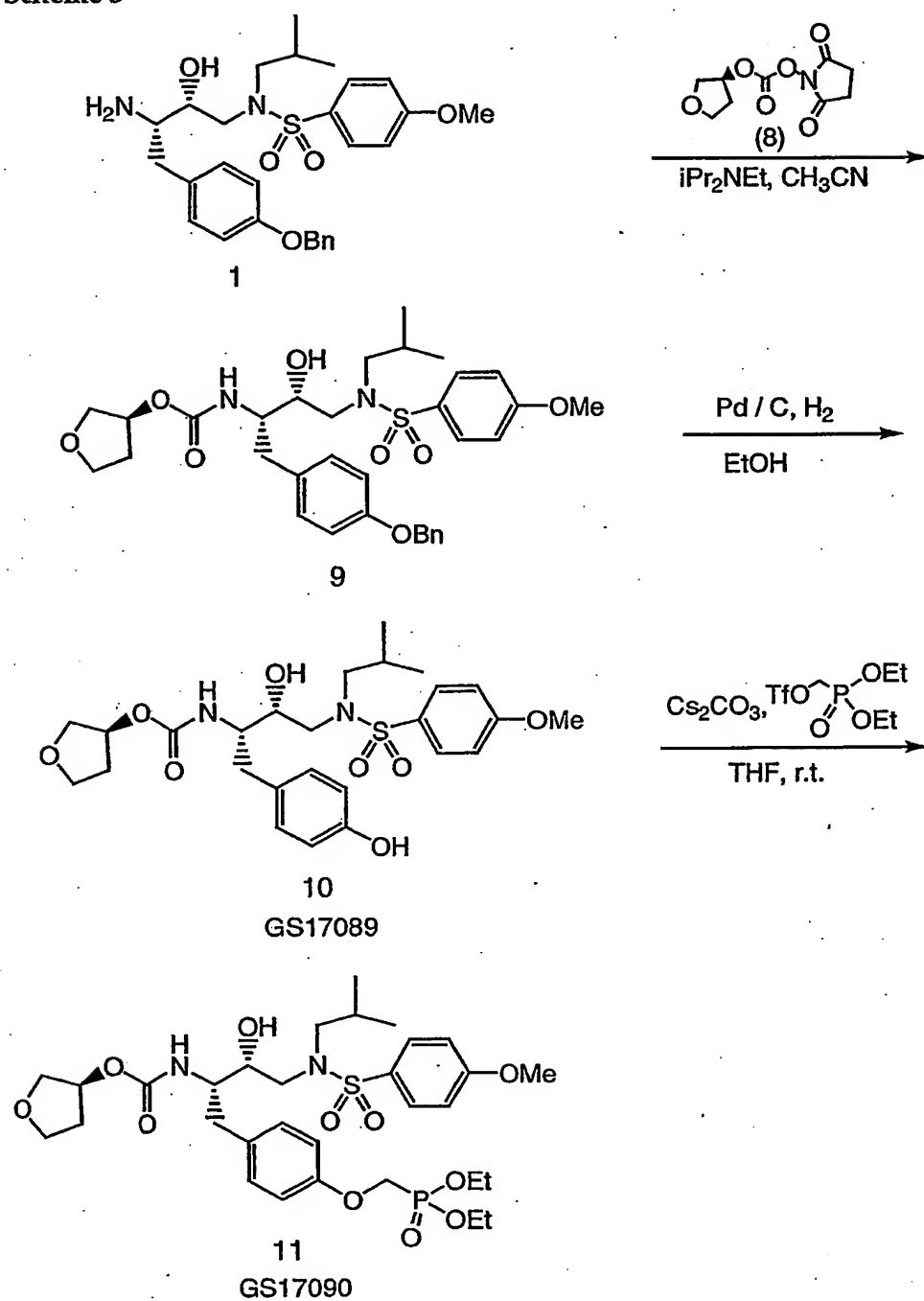
5

GS16573

Scheme 2

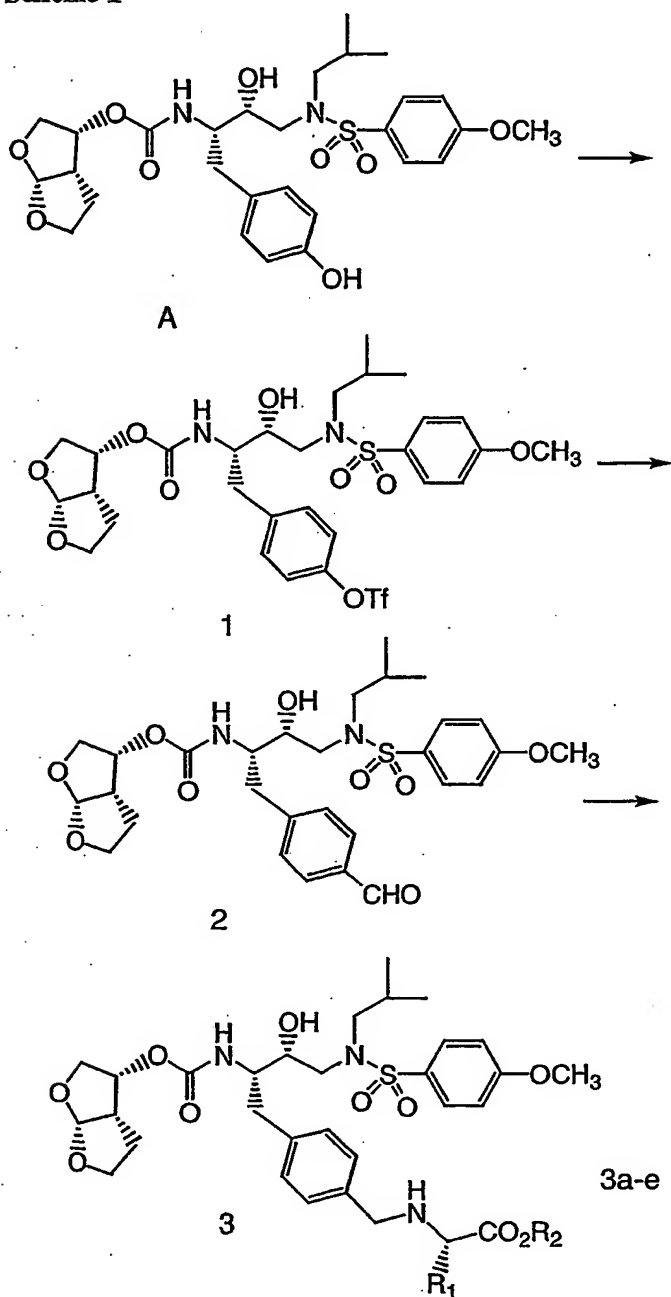


## Scheme 3



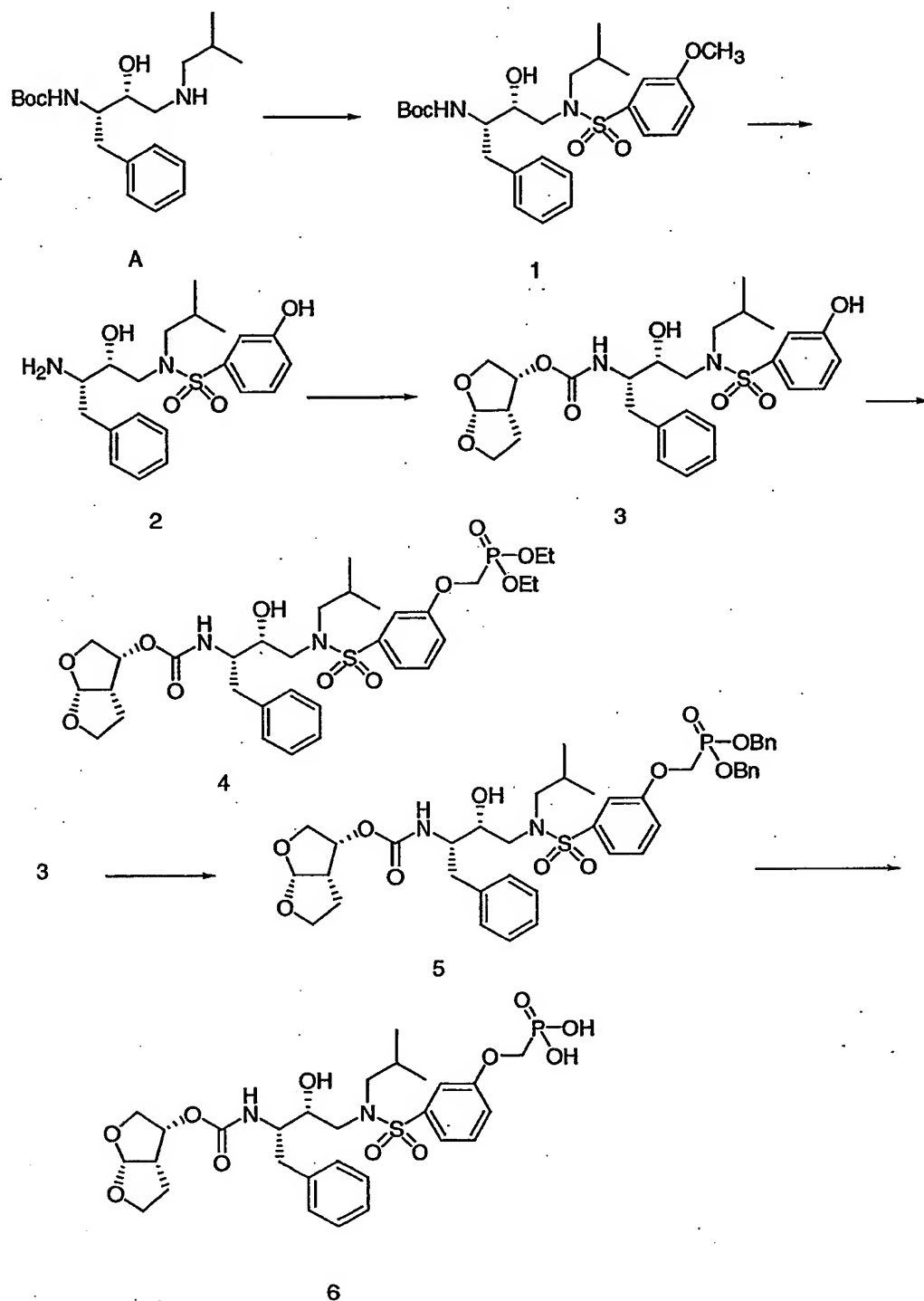
**Scheme Section I**

Schemes 1-4 are described in the examples.

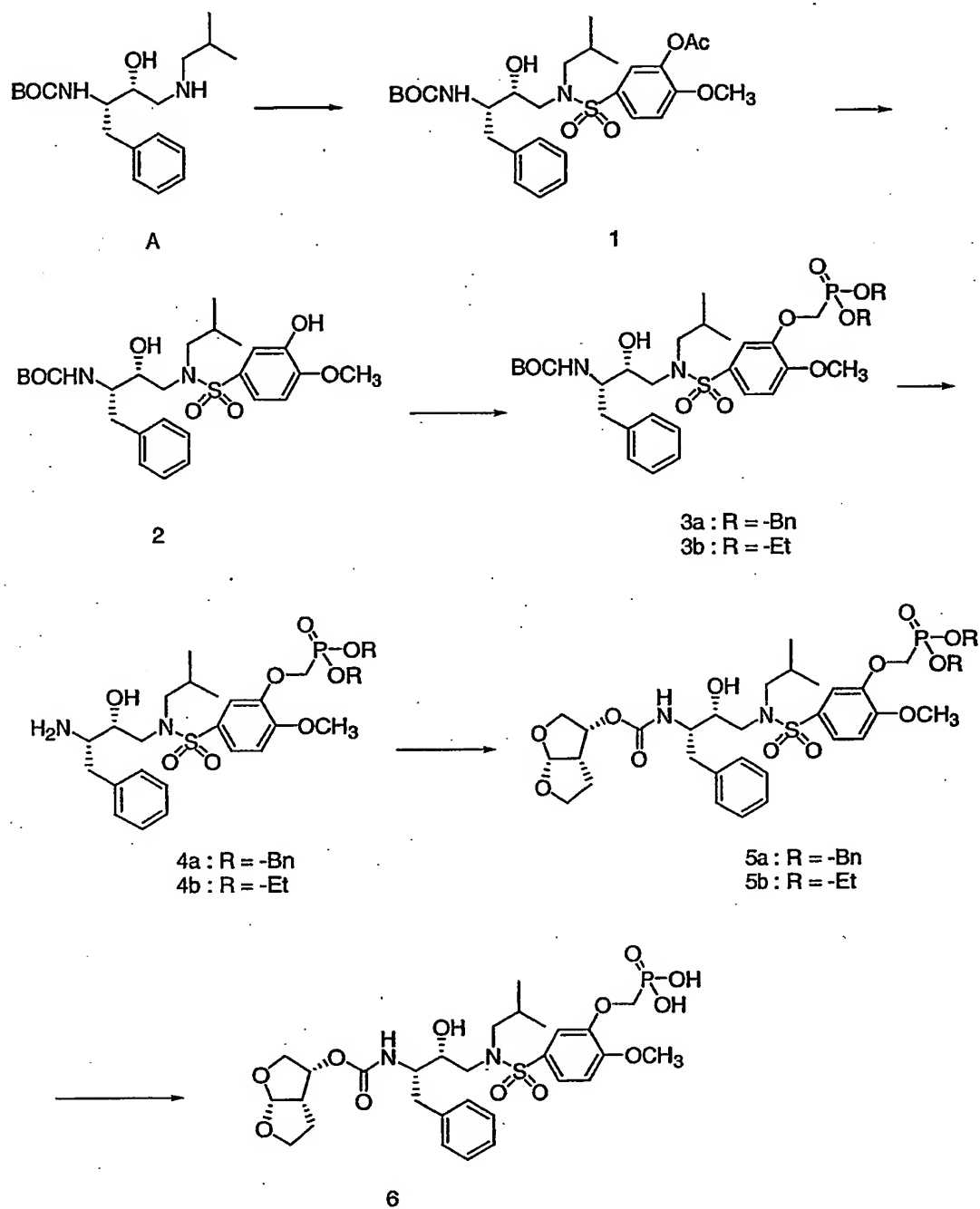
**Scheme 1**



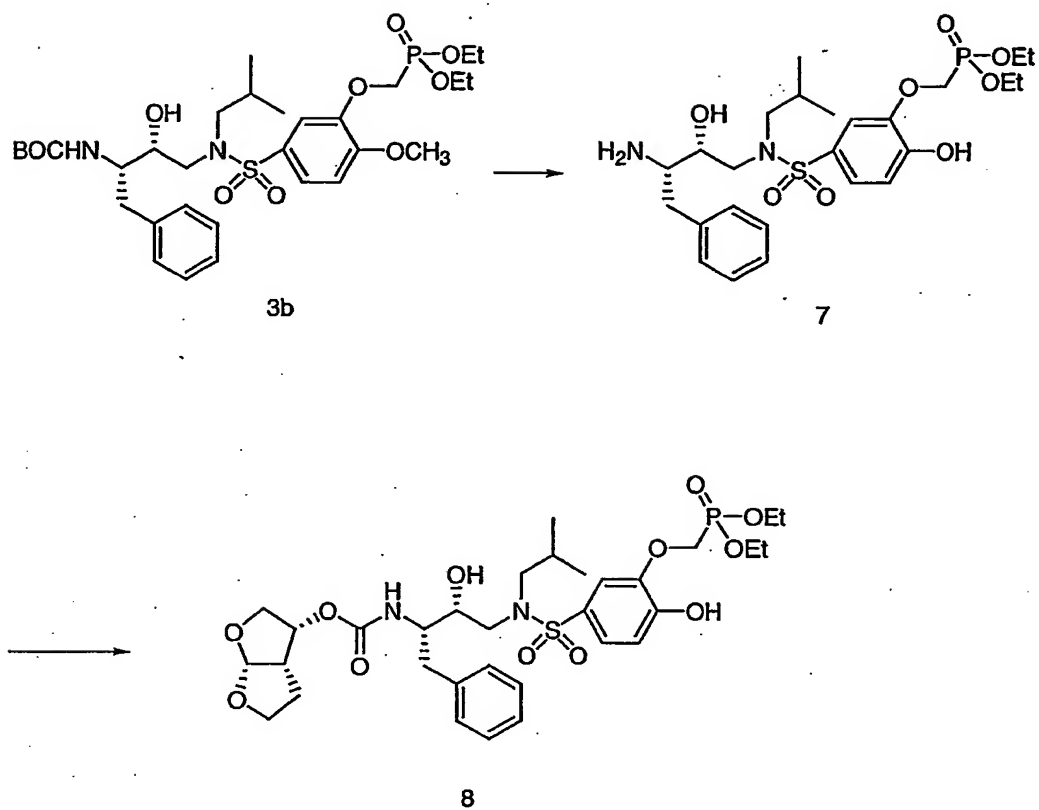
## Scheme 2



## Scheme 3



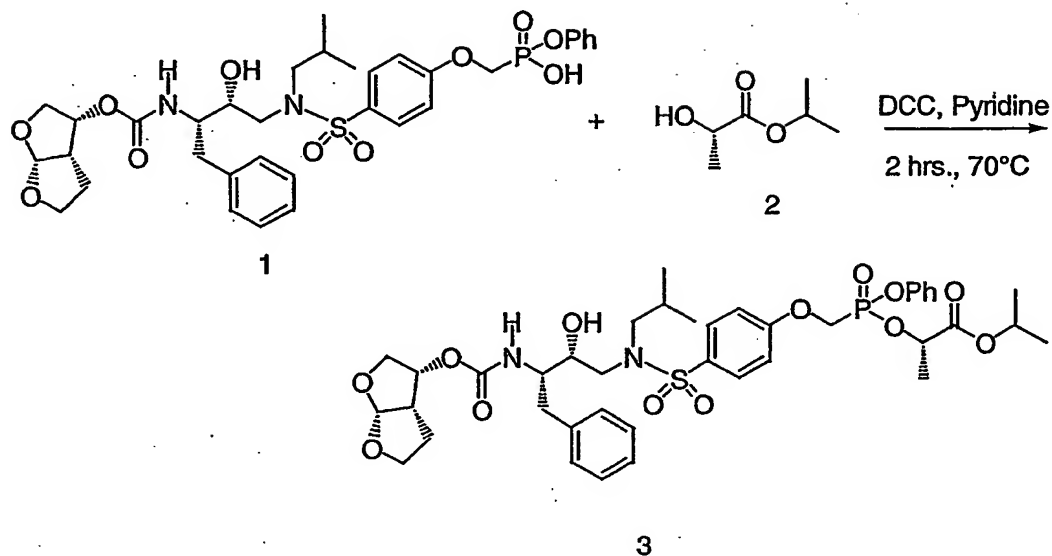
## Scheme 4



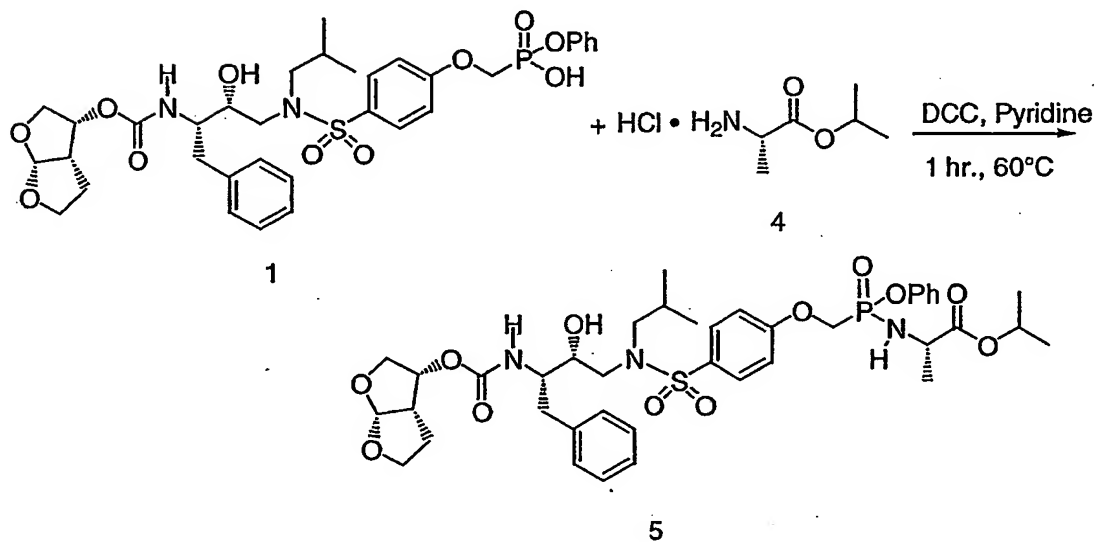
## Scheme Section K

Schemes 1-9 are described in the examples.

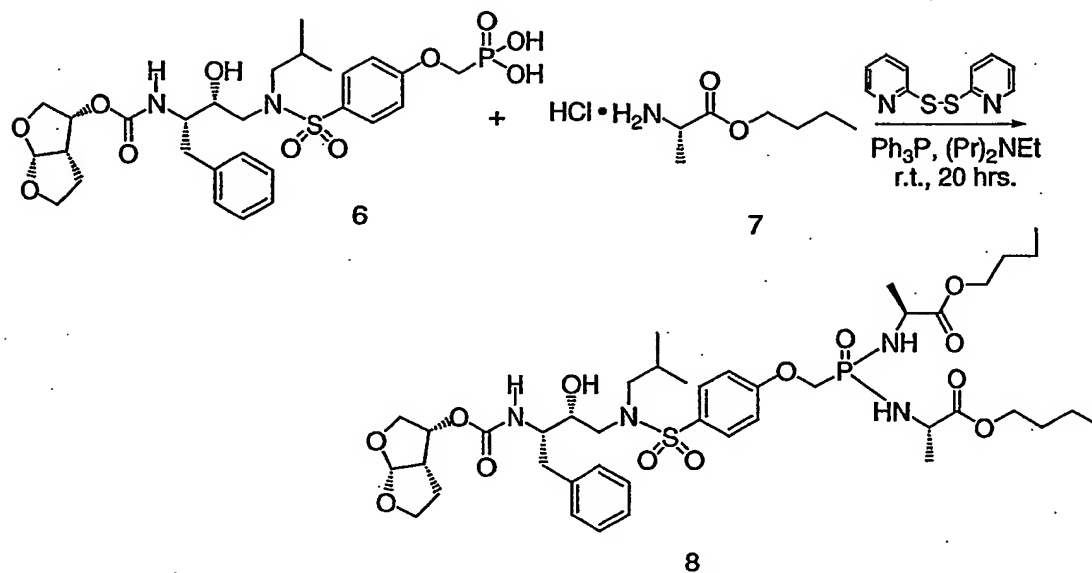
## 5 Scheme 1



## 10 Scheme 2

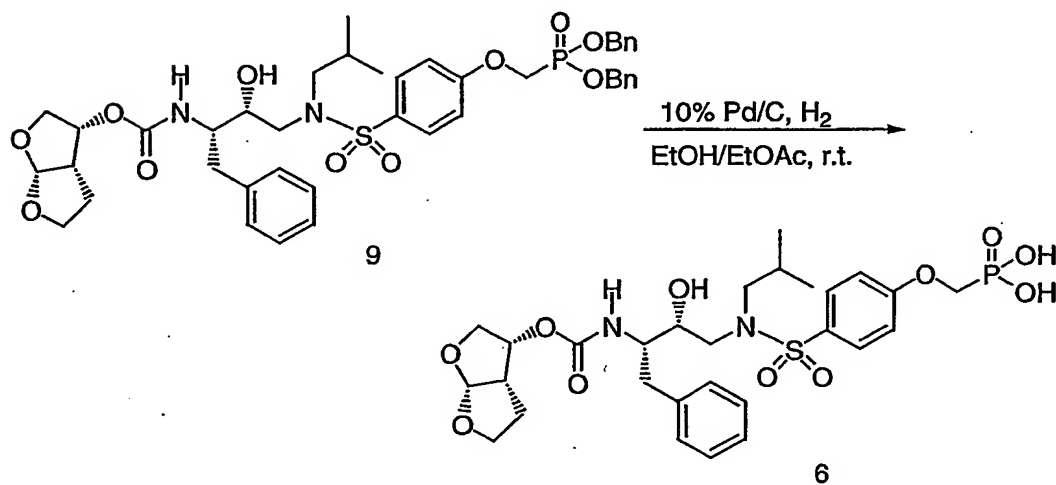


## Scheme 3

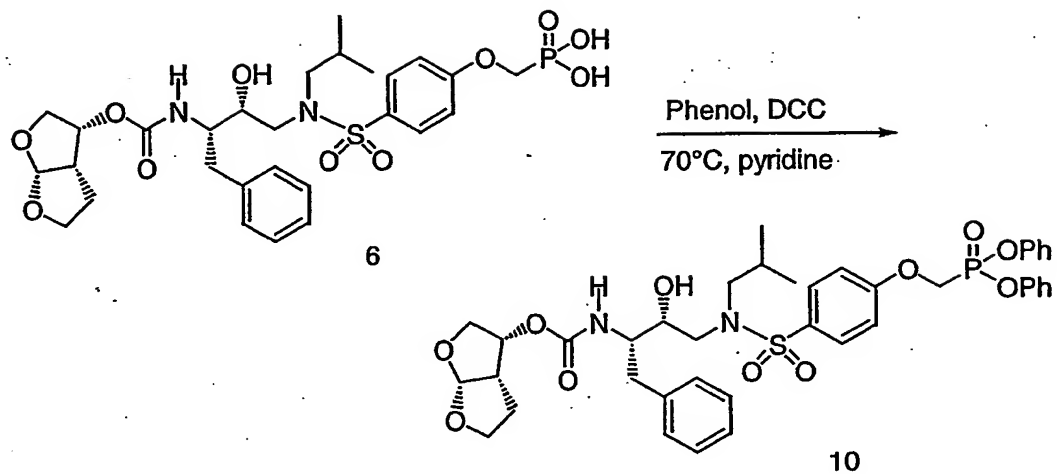


## Scheme 4

5

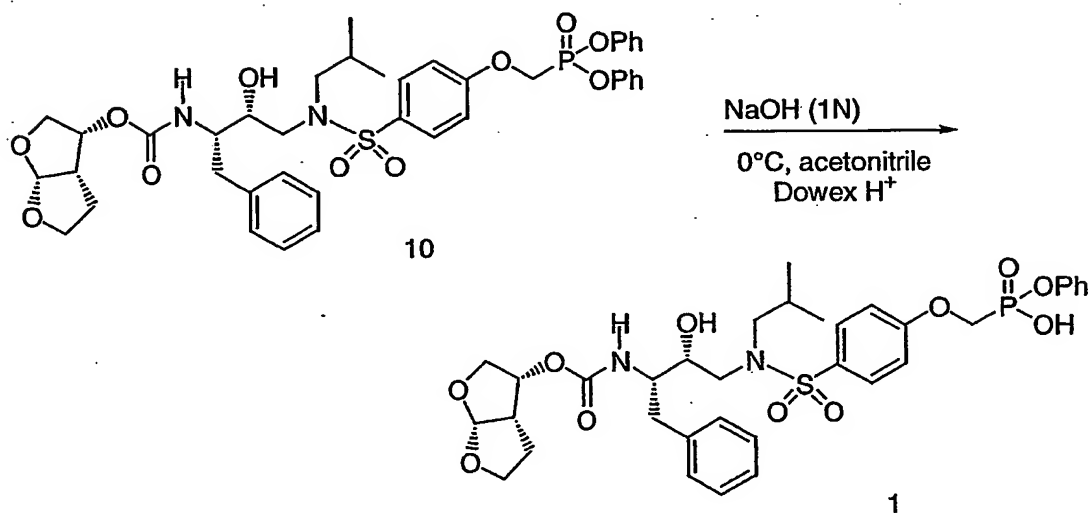


## Scheme 5

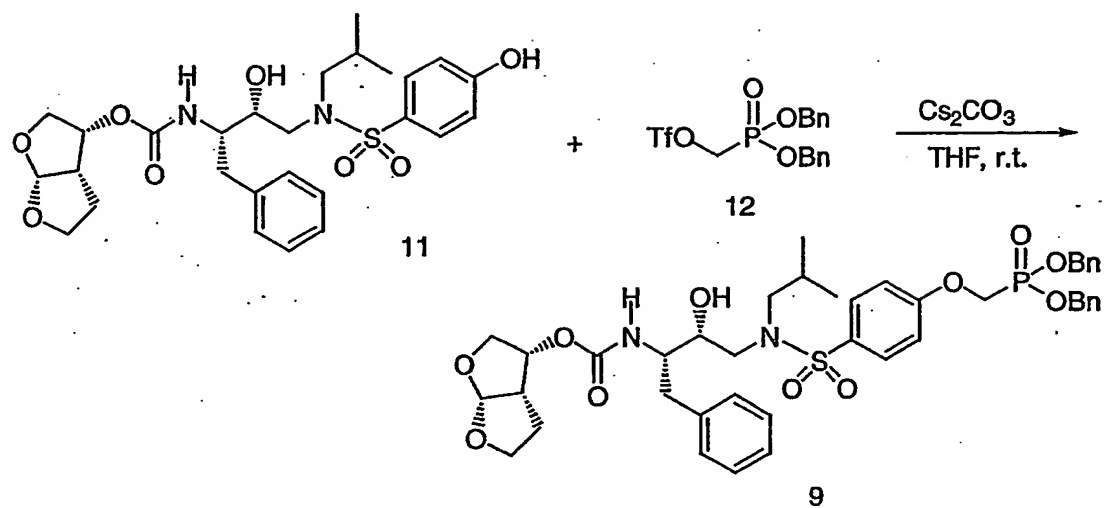


5

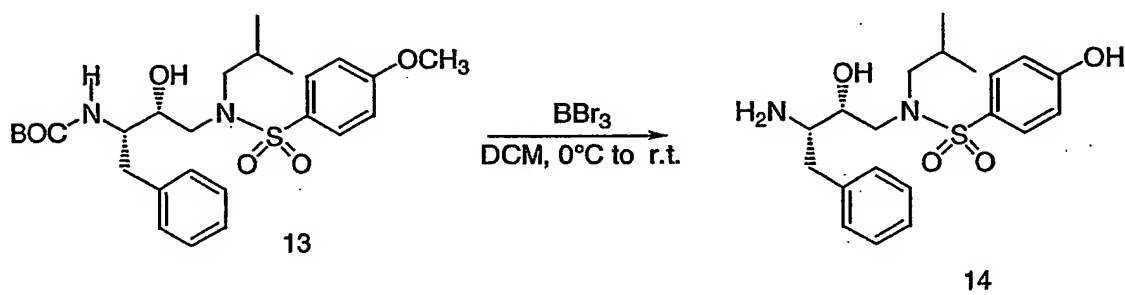
## Scheme 6



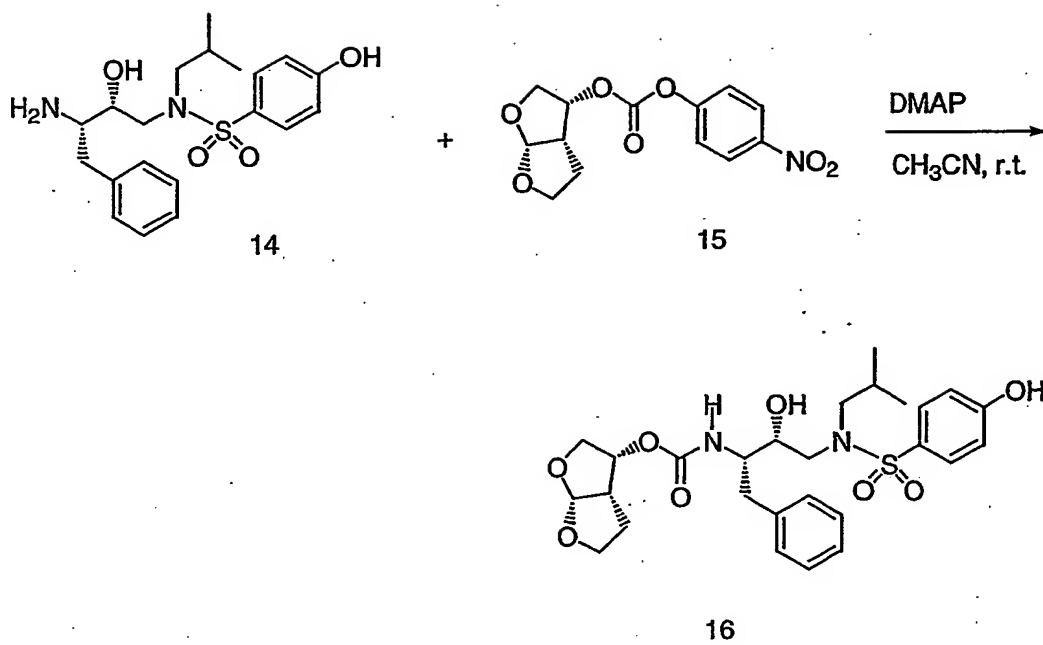
## Scheme 7



## 5 Scheme 8



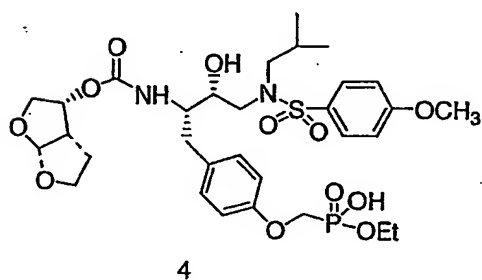
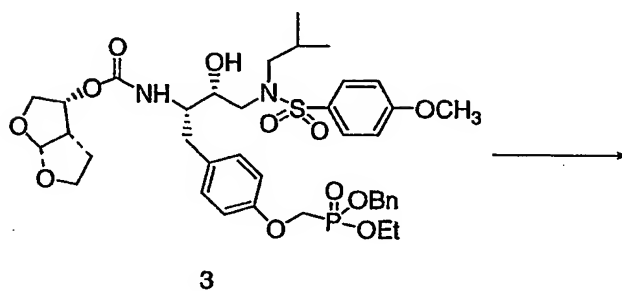
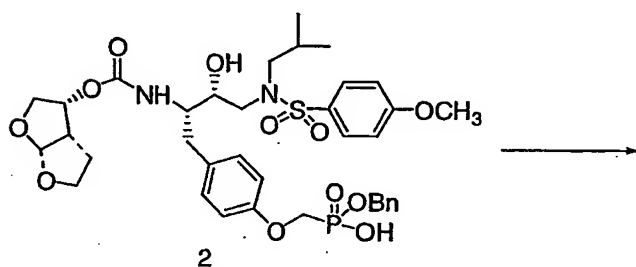
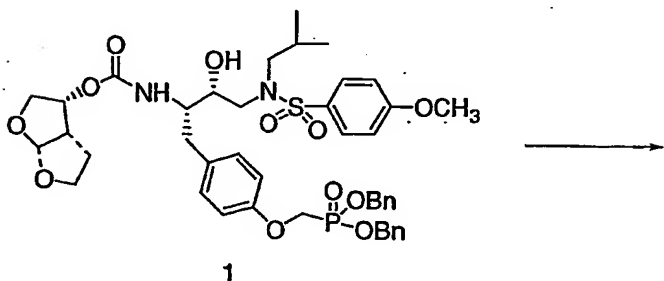
Scheme 9



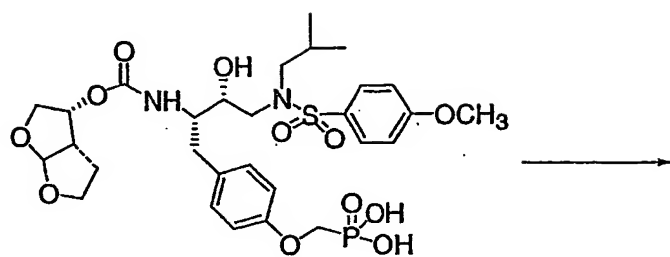


**Scheme Section L**

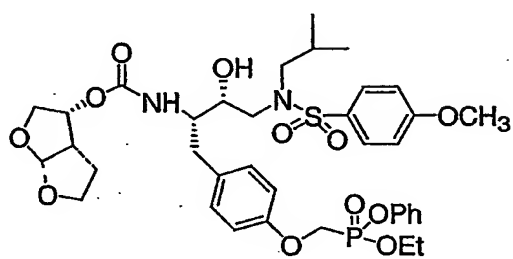
Schemes 1-9 are described in the examples.

**Scheme 1****Synthesis of P1-Phosphonic ester**

## Scheme 2



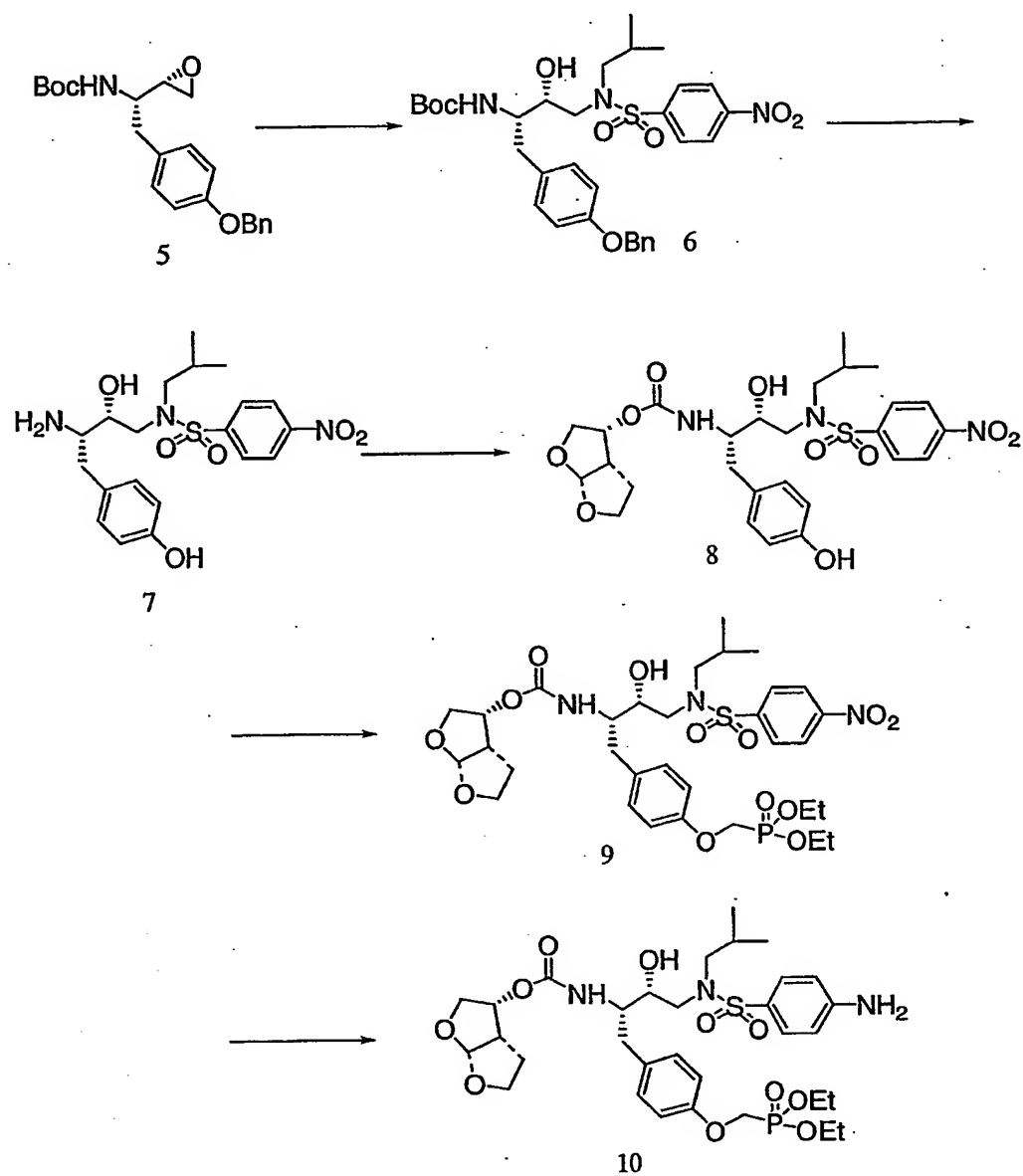
11



5

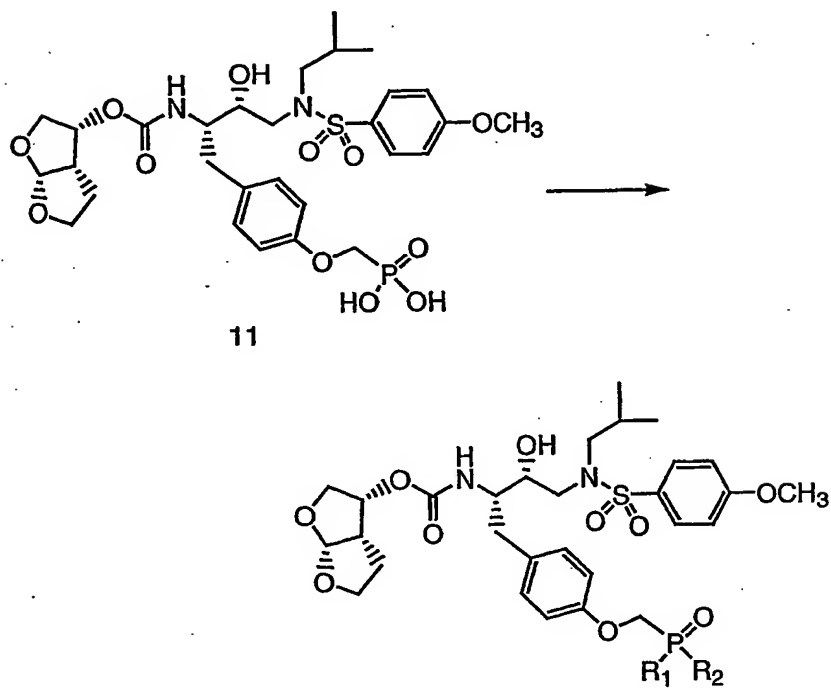
## Scheme 3

## Synthesis of P2'-Amino-P1-Phosphonic ester



## Scheme 4

## Synthesis of Bisamidates



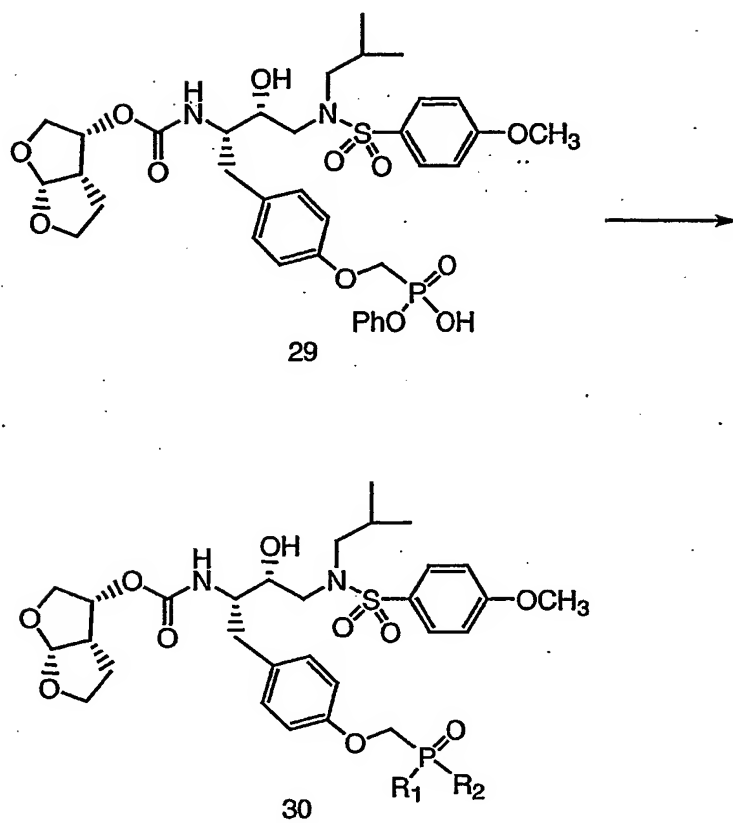
16 a,b,j and k

5

Compound	R <sub>1</sub>	R <sub>2</sub>
16a	Gly-Et	Gly-Et
16b	Gly-Bu	Gly-Bu
16j	Phe-Bu	Phe-Bu
16k	NHEt	NHEt

## Scheme 5

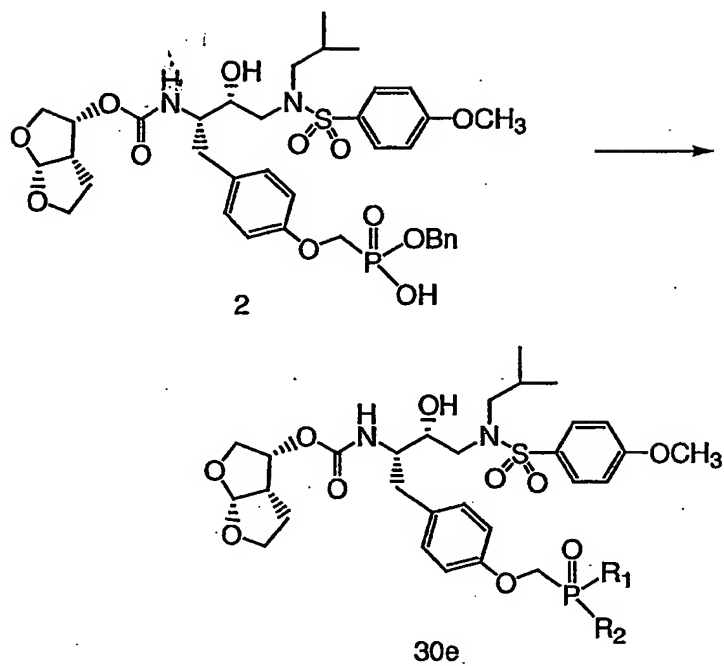
## Synthesis of Monoamidates



5

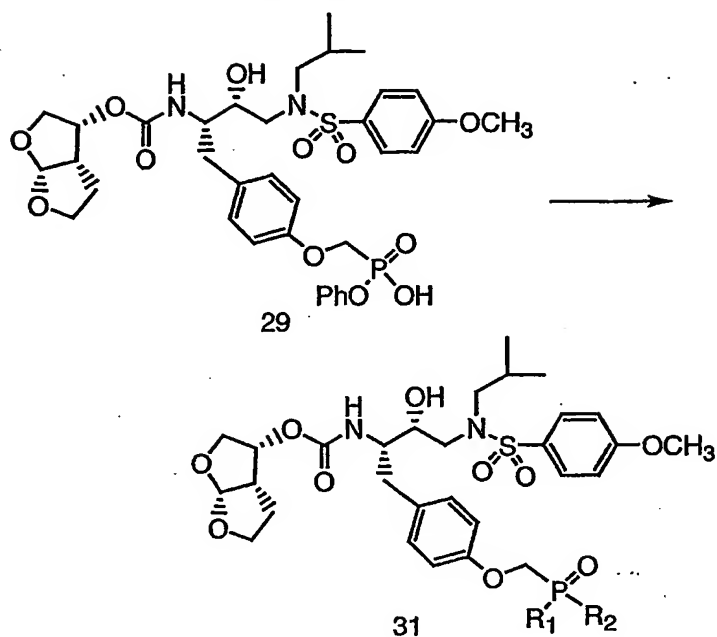
Compound	R <sub>1</sub>	R <sub>2</sub>
30a	OPh	Ala-Me
30b	OPh	Ala-Et
30c	OPh	(D)-Ala-iPr
30d	OPh	Ala-Bu
30e	OBn	Ala-Et

## Scheme 6



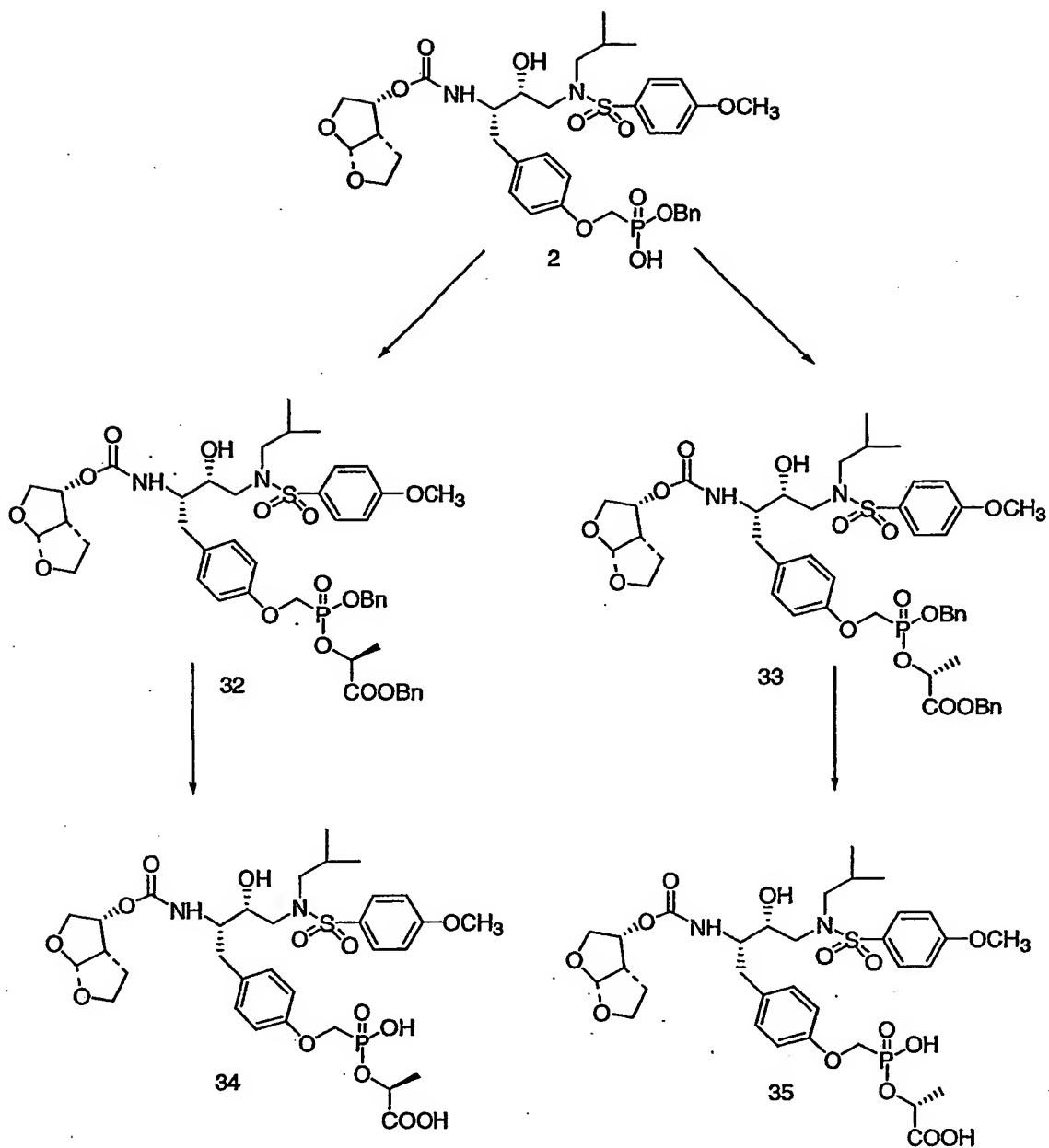
## Scheme 7

## Synthesis of Lactates



Compound	$R_1$	$R_2$
31a	OPh	Lac-iPr
31b	OPh	Lac-Et
31c	OPh	Lac-Bu
31d	OPh	(R)-Lac-Me
31e	OPh	(R)-Lac-Et

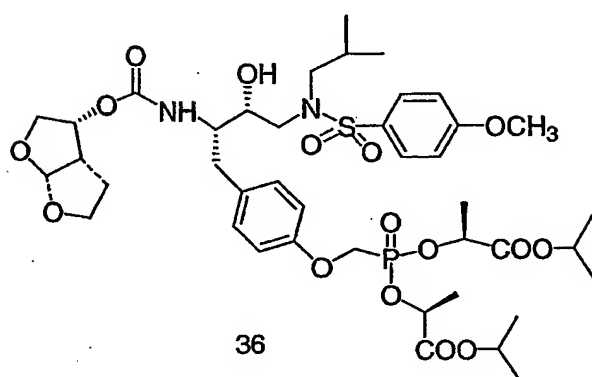
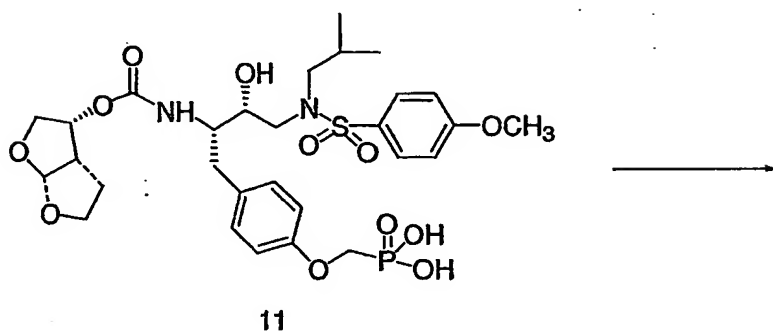
Scheme 8





## Scheme 9

## Synthesis of Bislactate



## Examples

The following Examples refer to the Schemes.

- 5 Some Examples have been performed multiple times. In repeated Examples, reaction conditions such as time, temperature, concentration and the like, and yields were within normal experimental ranges. In repeated Examples where significant modifications were made, these have been noted where the results varied significantly from those described. In Examples where different starting materials were used, these are noted. When the repeated
- 10 Examples refer to a "corresponding" analog of a compound, such as a "corresponding ethyl ester", this intends that an otherwise present group, in this case typically a methyl ester, is taken to be the same group modified as indicated.

### Example Section A

15 Example 1

Diazo ketone 1: To a solution of N-tert-Butoxycarbonyl-O-benzyl-L-tyrosine (11 g, 30 mmol, Fluka) in dry THF (55 mL) at -25-30°C (external bath temperature) was added isobutylchloroformate (3.9 mL, 30 mmol) followed by the slow addition of N-methylmorpholine (3.3 mL, 30 mmol). The mixture was stirred for 25 min, filtered while

20 cold, and the filter cake was rinsed with cold (0°C) THF (50 mL). The filtrate was cooled to -25°C and diazomethane (~50 mmol, generated from 15 g Diazald according to Aldrichimica Acta 1983, 16, 3) in ether (~150 mL) was poured into the mixed anhydride solution. The reaction was stirred for 15 min and was then placed in an icebath at 0°C, allowing the bath to warm to room temperature while stirring overnight for 15 h. The solvent was evaporated

25 under reduced pressure and the residue was dissolved in EtOAc, washed with water, saturated NaHCO<sub>3</sub>, saturated NaCl, dried (MgSO<sub>4</sub>), filtered and evaporated to a pale yellow solid. The crude solid was slurried in hexane, filtered, and dried to afford the diazo ketone (10.9 g, 92%) which was used directly in the next step.

30 Example 2

Chloroketone 2: To a suspension of diazoketone 1 (10.8 g, 27 mmol) in ether (600 mL) at 0°C was added 4M HCl in dioxane (7.5 mL, 30 mmol). The solution was removed from the cooling bath, and allowed to warm to room temperature at which time the reaction was stirred 1 h. The reaction solvent was evaporated under reduced pressure to give a solid residue that

was dissolved in ether and passed through a short column of silica gel. The solvent was evaporated to afford the chloroketone (10.7 g, 97%) as a solid.

### Example 3

5 Chloroalcohol 3: To a solution of chloroketone 2 (10.6 g, 26 mmol) in THF (90 mL) was added water (10 mL) and the solution was cooled to 3-4°C (internal temperature). A solution of NaBH<sub>4</sub> (1.5 g, 39 mmol) in water (5 mL) was added dropwise over a period of 10 min. The mixture was stirred for 1h at 0°C and saturated KHSO<sub>4</sub> was slowly added until the pH<4 followed by saturated NaCl. The organic phase was washed with saturated NaCl, dried  
10 (MgSO<sub>4</sub>) filtered and evaporated under reduced pressure. The crude product consisted of a 70:30 mixture of diastereomers by HPLC analysis (mobile phase, 77:25-CH<sub>3</sub>CN:H<sub>2</sub>O; flow rate: 1 mL/min; detection: 254 nm; sample volume: 20 µL; column: 5µ C18, 4.6X250 mm, Varian; retention times: major diastereomer 3, 5.4 min, minor diastereomer 4, 6.1 min). The residue was recrystallized from EtOAc/hexane twice to afford the chloro alcohol 3 (4.86g,  
15 >99% diastereomeric purity by HPLC analysis) as a white solid.

### Example 4

Epoxide 5: A solution of chloroalcohol 3 (4.32 g, 10.6 mmol) in EtOH (250 mL) and THF (100 mL) was treated with K<sub>2</sub>CO<sub>3</sub> (4.4g, 325 mesh, 31.9 mmol) and the mixture was stirred  
20 for at room temperature for 20h. The reaction mixture was filtered and was evaporated under reduced pressure. The residue was partitioned between EtOAc and water and the organic phase was washed with saturated NaCl, dried (MgSO<sub>4</sub>), filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel to afford the epoxide  
(3.68 g, 94%) as a white solid.

25

### Example 5

Sulfonamide 6: To a suspension of epoxide 5 (2.08 g, 5.6 mmol) in 2-propanol (20 mL) was added isobutylamine (10.7 mL, 108 mmol) and the solution was refluxed for 30 min. The solution was evaporated under reduced pressure and the crude solid was dissolved in CH<sub>2</sub>Cl<sub>2</sub>  
30 (20 mL) and cooled to 0°C. N,N'-diisopropylethylamine (1.96 mL, 11.3 mmol) was added followed by the addition of 4-methoxybenzenesulfonyl chloride (1.45 g, 7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and the solution was stirred for 40 min at 0°C, warmed to room temperature and

evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaHCO<sub>3</sub>. The organic phase was washed with saturated NaCl, dried (MgSO<sub>4</sub>), filtered and evaporated under reduced pressure. The crude product was recrystallized from EtOAc/hexane to give the sulfonamide (2.79 g, 81%) as a small white needles: mp 122-124°C (uncorrected).

#### Example 6

Carbamate 7: A solution of sulfonamide 6 (500 mg, 0.82 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) at 0°C was treated with trifluoroacetic acid (5 mL). The solution was stirred at 0°C for 30 min and was removed from the cold bath stirring for an additional 30 min. Volatiles were evaporated under reduced pressure and the residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and saturated NaHCO<sub>3</sub>. The aqueous phase was extracted twice with CH<sub>2</sub>Cl<sub>2</sub> and the combined organic extracts were washed with saturated NaCl, dried (MgSO<sub>4</sub>), filtered, and evaporated under reduced pressure. The residue was dissolved in CH<sub>3</sub>CN (5 mL) and was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (263 mg, 0.89 mmol, prepared according to Ghosh et al., J. Med. Chem. 1996, 39, 3278.) and N,N-dimethylaminopyridine (197 mg, 1.62 mmol). After stirring for 1.5h at room temperature, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 5% citric acid. The organic phase was washed twice with 1% K<sub>2</sub>CO<sub>3</sub>, and then was washed with saturated NaCl, dried (MgSO<sub>4</sub>), filtered, and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (1/1 - EtOAc/hexane) affording the carbamate (454 mg, 83%) as a solid: mp 128-129°C (MeOH, uncorrected).

#### Example 7

Phenol 8: A solution of carbamate 7 (1.15 g, 1.7 mmol) in EtOH (50 mL) and EtOAc (20 mL) was treated with 10% Pd/C (115 mg) and was stirred under H<sub>2</sub> atmosphere (balloon) for 18h. The reaction solution was purged with N<sub>2</sub>, filtered through a 0.45 µM filter and was evaporated under reduced pressure to afford the phenol as a solid that contained residual solvent: mp 131-134°C (EtOAc/hexane, uncorrected).

#### Example 8

Dibenzylphosphonate 10: To a solution of dibenzylhydroxymethyl phosphonate (527 mg, 1.8 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) was treated with 2,6-lutidine (300  $\mu\text{L}$ , 2.6 mmol) and the reaction flask was cooled to  $-50^\circ\text{C}$  (external temperature). Trifluoromethanesulfonic anhydride (360  $\mu\text{L}$ , 2.1 mmol) was added and the reaction mixture was stirred for 15 min and then the cooling bath was allowed to warm to  $0^\circ\text{C}$  over 45 min. The reaction mixture was partitioned between ether and ice-cold water. The organic phase was washed with cold 1M  $\text{H}_3\text{PO}_4$ , saturated NaCl, dried ( $\text{MgSO}_4$ ), filtered and evaporated under reduced pressure to afford triflate 9 (697 mg, 91%) as an oil which was used directly without any further purification. To a solution of phenol 8 (775 mg, 1.3 mmol) in THF (5 mL) was added  $\text{Cs}_2\text{CO}_3$  (423 mg, 1.3 mmol) and triflate 9 (710 mg, 1.7 mmol) in THF (2 mL). After stirring the reaction mixture for 30 min at room temperature additional  $\text{Cs}_2\text{CO}_3$  (423 mg, 1.3 mmol) and triflate (178 mg, 0.33 mmol) were added and the mixture was stirred for 3.5h. The reaction mixture was evaporated under reduced pressure and the residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried ( $\text{MgSO}_4$ ), filtered and evaporated under reduced pressure. The crude product was chromatographed on silica gel eluting (5% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the dibenzylphosphonate as an oil that solidified upon standing. The solid was dissolved in EtOAc, ether was added, and the solid was precipitated at room temperature overnight. After cooling to  $0^\circ\text{C}$ , the solid was filtered and washed with cold ether to afford the dibenzylphosphonate (836 mg, 76%) as a white solid:

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.66 (d, 2H), 7.31 (s, 10H), 7.08 (d, 2H), 6.94 (d, 2H), 6.76 (d, 2H), 5.59 (d, 1H), 5.15-4.89 (m, 6H), 4.15 (d, 2H), 3.94-3.62 (m, 10H), 3.13-2.69 (m, 7H), 1.78 (m, 1H), 1.70-1.44 (m, 2H), 0.89-0.82 (2d, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  18.7; MS (ESI) 853 (M+H).

#### Example 9

Phosphonic acid 11: A solution of dibenzylphosphonate 10 (0.81 g) was dissolved in EtOH/EtOAc (30mL/10 mL), treated with 10% Pd/C (80 mg) and was stirred under  $\text{H}_2$  atmosphere (balloon) for 1.5h. The reaction was purged with  $\text{N}_2$ , and the catalyst was removed by filtration through celite. The filtrate was evaporated under reduced pressure and the residue was dissolved in MeOH and filtered with a 0.45  $\mu\text{m}$  filter. After evaporation of the filtrate, the residue was triturated with ether and the solid was collected by filtration to afford the phosphonic acid (634 mg, 99%) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.77 (d, 2H), 7.19 (d, 2H), 7.09 (d, 2H), 6.92 (d, 2H), 5.60 (d, 1H), 4.95 (m, 1H), 4.17 (d, 2H), 3.94 (m, 1H), 3.89

(s, 3H), 3.85-3.68 (m, 5H), 3.42 (dd, 1H), 3.16-3.06 (m, 2H), 2.96-2.84 (m, 3H), 2.50 (m, 1H), 2.02 (m, 1H), 1.58 (m, 1H), 1.40 (dd, 1H), 0.94 (d, 3H), 0.89 (d, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  16.2; MS (ESI) 671 (M-H).

#### 5 Example 10

Diethylphosphonate 13: Triflate 12 was prepared from diethyl hydroxymethylphosphonate (2g, 11.9 mmol), 2,6-lutidine (2.1 mL, 17.9 mmol), and trifluoromethanesulfonic anhydride (2.5 mL, 14.9 mmol) as described for compound 9. To a solution of phenol 8 (60 mg, 0.10 mmol) in THF (2 mL) was added  $\text{Cs}_2\text{CO}_3$  (65mg, 0.20 mmol) and triflate 12 (45 mg, 0.15 mmol) in THF (0.25 mL). The mixture was stirred at room temperature for 2h and additional triflate (0.15 mmol) in THF (0.25 mL) was added. After 2h the reaction mixture was partitioned between EtOAc and saturated NaCl. The organic phase was dried ( $\text{MgSO}_4$ ), filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (EtOAc) to give a residue that was purified by chromatography on silica gel (5% 2-propanol /  $\text{CH}_2\text{Cl}_2$ ) to afford the diethylphosphonate as a foam:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.66 (d, 2H), 7.10 (d, 2H), 6.94 (d, 2H), 6.82 (d, 2H), 5.60 (d, 1H), 4.97 (d, 2H), 4.23-4.13 (m, 6H), 3.93-3.62 (m, 10H), 3.12-2.68 (m, 7H), 1.84-1.44 (m, 3H), 1.31 (t, 6H), 0.88-0.82 (2d, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.7; MS (ESI) 729 (M+H).

#### 20 Example 11

Diphenylphosphonate 14: To a solution of 11 (100mg, 0.15 mmol) and phenol (141 mg, 1.5 mmol) in pyridine (1.5 mL) was added N, N-diisopropylcarbodiimide (50  $\mu\text{L}$ , 0.38 mmol). The solution was stirred for 31h at room temperature and for 20h at 50°C. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel eluting (EtOAc) to provide diphenylphosphonate 14 (16 mg) as a foam:  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  10.9; MS (ESI) 847 (M+Na).

#### Example 12

Bis-Poc-phosphonate 15: To a solution of 11 (50 mg, 0.74 mmol) and isopropylchloromethyl carbonate (29 mg, 0.19 mmol) in DMF (0.5 mL) was added triethylamine (26  $\mu\text{L}$ , 0.19 mmol) and the solution was heated at 70°C (bath temperature) for 4.5h. The reaction was concentrated under reduced pressure and the residue was purified by preparative layer

chromatography (2% 2-propanol/ CH<sub>2</sub>Cl<sub>2</sub>) to afford 15 (7 mg): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.71 (d, 2H), 7.15 (d, 2H); 7.01 (d, 2H), 6.93 (d, 2H), 5.80-5.71 (m, 4H), 5.67 (d, 1H), 5.07-4.87 (m, 4H), 4.35 (d, 2H), 4.04-3.68 (m, 10H), 3.13 (dd, 1H), 3.04-2.90 (m, 5H), 2.79 (dd, 1H), 1.88-1.50 (m, 3H+H<sub>2</sub>O peak), 1.30 (m, 12H), 0.93 (d, 3H), 0.88 (d, 3H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 19.6.

5

### Example 13

Synthesis of Bisamidates 16a-j. Representative Procedure, Bisamidate 16f: A solution of phosphonic acid 11 (100 mg, 0.15 mmol) and (S)-2-aminobutyric acid butyl ester hydrochloride (116 mg, 0.59 mmol) was dissolved in pyridine (5 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph<sub>3</sub>P (117 mg, 0.45 mmol) and 2,2'-dipyridyl disulfide (98 mg, 0.45 mmol) in pyridine (1 mL) stirring for 20h at room temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (1% to 5% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>). The purified product was suspended in ether and was evaporated under reduced pressure to afford bisamidate 16f (106 mg, 75%) as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.72 (d, 2H), 7.15 (d, 2H), 7.01 (d, 2H), 6.87 (d, 2H), 5.67 (d, 1H), 5.05 (m, 1H), 4.96 (d, 1H), 4.19-3.71 (m overlapping s, 18H), 3.42 (t, 1H), 3.30 (t, 1H), 3.20 (dd, 1H), 3.20-2.97 (m, 4H), 2.80 (dd, 2H), 1.87-1.54 (m, 19H), 1.42-1.35 (4H), 0.97-0.88 (m, 18H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 20.3; MS (ESI) 955 (M+H).

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Compound	R <sub>1</sub>	R <sub>2</sub>	Amino Acid
16a	H	Et	Gly
16b	H	Bu	Gly
16c	Me	Et	Ala
16d	Me	Bu	Ala
16e	Et	Et	Aba <sup>1</sup>
16f	Et	Bu	Aba <sup>1</sup>
16g	iBu	Et	Leu
16h	iBu	Bu	Leu
16i	Bn	Et	Phe
16j	Bn	Bu	Phe

<sup>1</sup> Aba, 2-aminobutyric acid

### Example 14

Diazo ketone 17: To a solution of N-tert-Butoxycarbonyl-p-bromo-L-phenylalanine (9.9 g, 28.8 mmol, Synthetech) in dry THF (55 mL) at -25-30°C (external bath temperature) was added isobutylchloroformate (3.74 mL, 28.8 mmol) followed by the slow addition of N-

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methyldmorpholine (3.16 mL, 28.8 mmol). The mixture was stirred for 25 min, filtered while cold, and the filter cake was rinsed with cold (0°C) THF (50 mL). The filtrate was cooled to -25°C and diazomethane (~50 mmol, generated from 15 g diazald according to Aldrichimica Acta 1983, 16, 3) in ether (~150 mL) was poured into the mixed anhydride solution. The reaction was stirred for 15 min and was then placed in an icebath at 0°C, allowing the bath to warm to room temperature while stirring overnight for 15 h. The solvent was evaporated under reduced pressure and the residue was suspended in ether, washed with water, saturated NaHCO<sub>3</sub>, saturated NaCl, dried (MgSO<sub>4</sub>), filtered and evaporated to a pale yellow solid. The crude solid was slurried in hexane, filtered, and dried to afford diazo ketone 17 (9.73 g, 90%) which was used directly in the next step.

#### Example 15

Chloroketone 18: To a solution of diazoketone 17 (9.73 g, 26 mmol) in ether (500 mL) at 0°C was added 4M HCl in dioxane (6.6 mL, 26 mmol). The solution was stirred for 1 h at 0°C and 4M HCl in dioxane (1 mL) was added. After 1h, the reaction solvent was evaporated under reduced pressure to afford the chloroketone 18 (9.79 g, 98%) as a white solid.

#### Example 16

Chloroalcohol 19: A solution of chloroketone 18 (9.79g, 26 mmol) in THF (180 mL) and water (16 mL) was cooled to 0°C (internal temperature). Solid NaBH<sub>4</sub> (2.5 g, 66 mmol) was added in several portions over a period of 15 min while maintaining the internal temperature below 5°C. The mixture was stirred for 45 min and saturated KHSO<sub>4</sub> was slowly added until the pH<3. The mixture was partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc and the combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>) filtered and evaporated under reduced pressure. The residue was dissolved in EtOAc, and was passed through a short column of silica gel, and the solvent was evaporated. The solid residue was recrystallized from EtOAc/hexane to afford the chloroalcohol 19 (3.84g) as a white solid.

#### Example 17

Epoxide 21: A partial suspension of chloroalcohol 19 (1.16g, 3.1 mmol) in EtOH (50 mL) was treated with K<sub>2</sub>CO<sub>3</sub> (2g, 14.5 mmol) and the mixture was stirred for 4 h at room



temperature. The reaction mixture was diluted with EtOAc, filtered, and the solvents were evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl, and the organic phase was dried (MgSO<sub>4</sub>), filtered, and evaporated under reduced pressure to afford epoxide 21 (1.05g, 92%) as a white crystalline solid.

5

#### Example 18

Sulfonamide 22: To a solution of epoxide 21 (1.05g, 3.1 mmol) in 2-propanol (40 mL) was added isobutylamine (6 mL, 61 mmol) and the solution was refluxed for 30 min. The solution was evaporated under reduced pressure and the crude solid was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and cooled to 0°C. Triethylamine (642 µL, 4.6 mmol) was added followed by the addition of (634 mg, 3.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and the solution was stirred for 2h at 0°C at which time the reaction solution was treated with additional triethylamine (1.5 mmol) and 4-methoxybenzenesulfonyl chloride (0.31 mmol). After 1.5 h, the reaction solution was evaporated under reduced pressure. The residue was partitioned between EtOAc and cold 1M H<sub>3</sub>PO<sub>4</sub>. The organic phase was washed with saturated NaHCO<sub>3</sub>, saturated NaCl, dried (MgSO<sub>4</sub>), filtered and the solvent was evaporated under reduced pressure. The crude product was purified on silica gel (15/1 - CH<sub>2</sub>Cl<sub>2</sub>/EtOAc) to afford 1.67g of a solid which was recrystallized from EtOAc/hexane to give sulfonamide 22 (1.54g, 86%) as a white crystalline solid.

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#### Example 19

Silyl ether 23: To a solution of the sulfonamide 22 (1.53g, 2.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (12 mL) at 0°C was added N,N-diisopropylethylamine (0.68 mL, 3.9 mmol) followed by tert-butyldimethylsilyl trifluoromethanesulfonate (0.75 mL, 3.3 mmol). The reaction solution was stirred for 1 h at 0°C and was warmed to room temperature, stirring for 17 h. Additional N,N-diisopropylethylamine (3.9 mmol) and tert-butyldimethylsilyl trifluoromethanesulfonate (1.6 mmol) was added, stirred for 2.5h, then heated to reflux for 3h and stirred at room temperature for 12 h. The reaction mixture was partitioned between EtOAc and cold 1M H<sub>3</sub>PO<sub>4</sub>. The organic phase was washed with saturated NaHCO<sub>3</sub>, saturated NaCl, and was dried (MgSO<sub>4</sub>), filtered and evaporated under reduced pressure. The crude product was purified on silica gel (2/1 - hexane/ether) to afford silyl ether 23 (780 mg, 43%) as an oil.

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#### Example 20

Phosphonate 24: A solution of 23 (260 mg, 0.37 mmol), triethylamine (0.52 mL, 3.7 mmol), and diethylphosphite (0.24 mmol, 1.85 mmol) in toluene (2 mL) was purged with argon and to the solution was added  $(\text{Ph}_3\text{P})_4\text{Pd}$  (43 mg, 10 mol%). The reaction mixture was heated at 110°C (bath temperature) for 6 h, and was then allowed to stir at room temperature for 12h.

5 The solvent was evaporated under reduced pressure and the residue was partitioned between ether and water. The aqueous phase was extracted with ether and the combined organic extracts were washed with saturated NaCl, dried ( $\text{MgSO}_4$ ), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (2/1 - ethyl acetate/hexane) to afford diethylphosphonate 24 (153 mg, 55%).

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#### Example 21

Phosphonic acid 26: To a solution of 24 (143 mg) in MeOH (5 mL) was added 4N HCl (2 mL). The solution was stirred at room temperature for 9h and was evaporated under reduced pressure. The residue was triturated with ether and the solid was collected by filtration to provide hydrochloride salt 25 (100 mg, 92%) as a white powder. To a solution of X (47 mg, 0.87 mmol) in  $\text{CH}_3\text{CN}$  (1 mL) at 0°C was added TMSBr (130  $\mu\text{L}$ , 0.97 mmol). The reaction was warmed to room temperature and stirred for 6.5h at which time TMSBr (0.87 mmol) was added and stirring was continued for 16h. The solution was cooled to 0°C and was quenched with several drops of ice-cold water. The solvents were evaporated under reduced pressure and the residue was dissolved in several milliliters of MeOH and treated with propylene oxide (2 mL). The mixture was heated to gentle boiling and evaporated. The residue was triturated with acetone and the solid was collected by filtration to give phosphonic acid 26 (32 mg, 76%) as a white solid.

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#### 25 Example 22

Phosphonate 27: To a suspension of 26 (32 mg, 0.66 mmol) in  $\text{CH}_3\text{CN}$  (1 mL) was added bis(trimethylsilyl)acetamide (100  $\mu\text{L}$ , 0.40 mmol) and the solution was stirred for 30 min at room temperature. The solvent was evaporated under reduced pressure and the residue was dissolved in  $\text{CH}_3\text{CN}$  (1 mL). To this solution was added (3R, 3aR, 6aS)-hexahydrofuro[2, 3-b]furan-2-yl 4-nitrophenyl carbonate (20 mg, 0.069 mmol, prepared according to Ghosh et al. J. Med. Chem. 1996, 39, 3278.), N,N-diisopropylethylamine (35  $\mu\text{L}$ , 0.20 mmol), and N,N-dimethylaminopyridine (catalytic amount). The solution was stirred for 22h at room temperature, diluted with water (0.5 mL) and was stirred with IR 120 ion exchange resin (325

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mg, H<sup>+</sup> form) until the pH was <2. The resin was removed by filtration, washed with methanol and the filtrate was concentrated under reduced pressure. The residue was dissolved in water, treated with solid NaHCO<sub>3</sub> until pH=8 and was evaporated to dryness. The residue was dissolved in water and was purified on C18 reverse phase chromatography eluting with water followed by 5%, 10% and 20% MeOH in water to give the disodium salt 27 (24 mg) as a pale yellow solid: <sup>1</sup>H NMR (D<sub>2</sub>O) δ 7.72 (d, 2H), 7.52 (dd, 2H), 7.13 (dd, 2H), 7.05 (d, 2H), 5.58 (d, 1H), 4.87 (m, 1H), 3.86-3.53 (m overlapping s, 10H), 3.22 (dd, 1H), 3.12-2.85 (6H), 2.44 (m, 1H), 1.83 (m, 1H), 1.61 (m, 1H), 1.12 (dd, 1H), 0.77 (m, 6H); <sup>31</sup>P NMR (D<sub>2</sub>O) δ 11.23 ; MS (ESI) 641 (M-H).

10

#### Example 23

Diethylphosphonate 28: To a solution of 25 (16 mg, 0.028 mmol) in CH<sub>3</sub>CN (0.5 mL) was added (3R, 3aR, 6aS)-hexahydrofuro[2, 3-b]furan-2-yl 4-nitrophenyl carbonate (9 mg, 0.031 mmol), N,N-diisopropylethylamine (20 μL, 0.11 mmol), and N,N-dimethylaminopyridine (catalytic amount). The solution was stirred at room temperature for 48 h and was then concentrated under reduced pressure. The residue was partitioned between EtOAc and saturated NaHCO<sub>3</sub>. The organic phase was washed with saturated NaHCO<sub>3</sub>, saturated NaCl, and was dried (MgSO<sub>4</sub>), filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (2.5-5% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>). The residue obtained was further purified by preparative layer chromatography (5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) followed by column chromatography on silica gel (10% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to afford diethylphosphonate 28 (7 mg) as a foam: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.72-7.66 (m, 4H), 7.32-7.28 (2H), 6.96 (d, 2H), 5.60 (d, 1H), 4.97 (m, 2H), 4.18-4.01 (m, 4H), 3.94-3.60 (m overlapping s, 10H), 3.15-2.72 (m, 7H), 1.78 (m, 1H), 1.61 (m+H<sub>2</sub>O, ~3H), 1.28 (t; 6H), 0.86 (m, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 18.6 ; MS (ESI) 699 (M+H).

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#### Prospective Example 24

Diphenyl phosphonate 14 is treated with aqueous sodium hydroxide to provide monophenyl phosphonate 29 according to the method found in J. Med. Chem. 1994, 37, 1857.

Monophenyl phosphonate 29 is then converted to the monoamidate 30 by reaction with an amino acid ester in the presence of Ph<sub>3</sub> and 2,2'-dipyridyl disulfide as described in the synthesis of bisamidate 16f. Alternatively, monoamidate 30 is prepared by treating 29 with an

30

amino acid ester and DCC. Coupling conditions of this type are found in Bull. Chem. Soc. Jpn. 1988, 61, 4491.

#### Example 25

- 5 Diazo ketone 1: To a solution of N-tert-Butoxycarbonyl-O-benzyl-L-tyrosine (25 g, 67 mmol, Fluka) in dry THF (150 mL) at -25-30°C (external bath temperature) was added isobutylchloroformate (8.9 mL, 69 mmol) followed by the slow addition of N-methylmorpholine (37.5 mL, 69 mmol). The mixture was stirred for 40 min, and
- 10 according to Aldrichimica Acta 1983, 16, 3) in ether (400 mL) was poured into the mixed anhydride solution. The reaction was stirred for 15 min allowing the bath to warm to room temperature while stirring overnight for 4 h. The mixture was bubbled with N<sub>2</sub> for 30 min., washed with water, saturated NaHCO<sub>3</sub>, saturated NaCl, dried (MgSO<sub>4</sub>), filtered and evaporated to a pale yellow solid. The crude solid was slurried in hexane, filtered, and dried
- 15 to afford the diazo ketone (26.8 g, 99%) which was used directly in the next step.

#### Example 26

- Chloroketone 2: To a suspension of diazoketone 1 (26.8 g, 67 mmol) in ether/THF (750 mL, 3/2) at 0°C was added 4M HCl in dioxane (16.9 mL, 67 mmol). The solution was stirred at
- 20 0°C for 2 hr. The reaction solvent was evaporated under reduced pressure to give the chloroketone (27.7 g, 97%) as a solid.

#### Example 27

- Chloroalcohol 3: To a solution of chloroketone 2 (127.1 g, 67 mmol) in THF (350 mL) was
- 25 added water (40 mL) and the solution was cooled to 3-4°C (internal temperature). NaBH<sub>4</sub> (6.3 g, 168 mmol) was added in portions. The mixture was stirred for 1h at 0°C and the solvents were removed. The mixture was diluted with ethyl acetate and saturated KHSO<sub>4</sub> was slowly added until the pH<4 followed by saturated NaCl. The organic phase was washed with saturated NaCl, dried (MgSO<sub>4</sub>) filtered and evaporated under reduced pressure. The
- 30 crude product consisted of a 70:30 mixture of diastereomers by HPLC analysis (mobile phase, 77:25-CH<sub>3</sub>CN:H<sub>2</sub>O; flow rate: 1 mL/min; detection: 254 nm; sample volume: 20 µL; column: 5µ C18, 4.6X250 mm, Varian; retention times: major diastereomer 3, 5.4 min, minor

diastereomer 4, 6.1 min). The residue was recrystallized from EtOAc/hexane twice to afford the chloro alcohol 3 (12.2g, >96% diastereomeric purity by HPLC analysis) as a white solid.

#### Example 28

- 5 Epoxide 5: To a solution of chloroalcohol 3 (12.17 g, 130 mmol) in EtOH (300 mL) was added KOH/EtOH solution (0.71N, 51 mL, 36 mmol). The mixture was stirred for at room temperature for 1.5h. The reaction mixture was evaporated under reduced pressure. The residue was partitioned between EtOAc and water and the organic phase was washed with saturated NH<sub>4</sub>Cl, dried (MgSO<sub>4</sub>), filtered, and evaporated under reduced pressure to afford  
10 the epoxide (10.8 g, 97%) as a white solid.

#### Example 29

- Sulfonamide 6: To a suspension of epoxide 5 (10.8 g, 30 mmol) in 2-propanol (100 mL) was added isobutylamine (129.8 mL, 300 mmol) and the solution was refluxed for 1 hr. The  
15 solution was evaporated under reduced pressure to give a crude solid. The solid (42 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (200 mL) and cooled to 0°C. Triethylamine (11.7 mL, 84 mmol) was added followed by the addition of 4-methoxybenzenesulfonyl chloride (8.68 g, 42 mmol) and the solution was stirred for 40 min at 0°C, warmed to room temperature and evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaHCO<sub>3</sub>.  
20 The organic phase was washed with saturated NaCl, dried (MgSO<sub>4</sub>), filtered and evaporated under reduced pressure. The crude product was recrystallized from EtOAc/hexane to give the sulfonamide (23.4 g, 91%) as a small white needles: mp 122-124°C (uncorrected).

#### Example 30

- 25 Carbamate 7: A solution of sulfonamide 6 (6.29 mg, 10.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was treated with trifluoroacetic acid (10 mL). The solution was stirred for 3 hr. Volatiles were evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase were washed with 0.5 N NaOH (2x), water (2x) and saturated NaCl, dried (MgSO<sub>4</sub>), filtered, and evaporated under reduced pressure. The residue was  
30 dissolved in CH<sub>3</sub>CN (60 mL), cooled to 0°C and was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-b]furan-2-yl 4-nitrophenyl carbonate (298.5 g, 10 mmol, prepared according to Ghosh et al. J. Med. Chem. 1996, 39, 3278.) and N,N-dimethylaminopyridine (2.4 g, 20 mmol). After stirring for 1h at 0°C, the reaction solvent was evaporated under

reduced pressure and the residue was partitioned between EtOAc and 5% citric acid. The organic phase was washed twice with 1% K<sub>2</sub>CO<sub>3</sub>, and then was washed with saturated NaCl, dried (MgSO<sub>4</sub>), filtered, and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (1/1 - EtOAc/hexane) affording the carbamate (5.4 g, 83%) as a solid: mp 128-129°C (MeOH, uncorrected).

#### Example 31

Phenol 8: A solution of carbamate 7 (5.4 g, 8.0 mmol) in EtOH (260 mL) and EtOAc (130 mL) was treated with 10% Pd/C (540 mg) and was stirred under H<sub>2</sub> atmosphere (balloon) for 3h. The reaction solution stirred with celite for 10 min, and passed through a pad of celite. The filtrate was evaporated under reduced pressure to afford the phenol as a solid (4.9 g) that contained residual solvent: mp 131-134°C (EtOAc/hexane, uncorrected).

#### Example 32

Dibenzylphosphonate 10: To a solution of dibenzylhydroxymethyl phosphonate (3.1 g, 10.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) was treated with 2,6-lutidine (1.8 mL, 15.6 mmol) and the reaction flask was cooled to -50°C (external temperature). Trifluoromethanesulfonic anhydride (2.11 mL, 12.6 mmol) was added and the reaction mixture was stirred for 15 min and then the cooling bath was allowed to warm to 0°C over 45 min. The reaction mixture was partitioned between ether and ice-cold water. The organic phase was washed with cold 1M H<sub>3</sub>PO<sub>4</sub>, saturated NaCl, dried (MgSO<sub>4</sub>), filtered and evaporated under reduced pressure to afford triflate 9 (3.6 g, 80%) as an oil which was used directly without any further purification. To a solution of phenol 8 (3.61 g, 6.3 mmol) in THF (90 mL) was added Cs<sub>2</sub>CO<sub>3</sub> (4.1 g, 12.6 mmol) and triflate 9 (4.1 g, 9.5 mmol) in THF (10 mL). After stirring the reaction mixture for 30 min at room temperature additional Cs<sub>2</sub>CO<sub>3</sub> (6.96 g, 3 mmol) and triflate (1.26 g, 3 mmol) were added and the mixture was stirred for 3.5h. The reaction mixture was evaporated under reduced pressure and the residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried (MgSO<sub>4</sub>), filtered and evaporated under reduced pressure. The crude product was chromatographed on silica gel eluting (5% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the dibenzylphosphonate as an oil that solidified upon standing. The solid was dissolved in EtOAc, ether was added, and the solid was precipitated at room temperature overnight. After cooling to 0°C the solid was filtered and washed with cold ether to afford the dibenzylphosphonate (3.43 g, 64%) as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.66

(d, 2H), 7.31 (s, 10H), 7.08 (d, 2H), 6.94 (d, 2H), 6.76 (d, 2H), 5.59 (d, 1H), 5.15-4.89 (m, 6H), 4.15 (d, 2H), 3.94-3.62 (m, 10H), 3.13-2.69 (m, 7H), 1.78 (m, 1H), 1.70-1.44 (m, 2H), 0.89-0.82 (2d, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  18.7; MS (ESI) 853 (M+H).

5 Example 33

Phosphonic acid 11: A solution of dibenzylphosphonate 10 (3.43 g) was dissolved in EtOH/EtOAc (150 mL/50 mL), treated with 10% Pd/C (350 mg) and was stirred under  $\text{H}_2$  atmosphere (balloon) for 3 h. The reaction mixture was stirred with celite, and the catalyst was removed by filtration through celite. The filtrate was evaporated under reduced pressure and the residue was dissolved in MeOH and filtered with a 0.45  $\mu\text{M}$  filter. After evaporation of the filtrate, the residue was triturated with ether and the solid was collected by filtration to afford the phosphonic acid (2.6 g, 94%) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.77 (d, 2H), 7.19 (d, 2H), 7.09 (d, 2H), 6.92 (d, 2H), 5.60 (d, 1H), 4.95 (m, 1H), 4.17 (d, 2H), 3.94 (m, 1H), 3.89 (s, 3H), 3.85-3.68 (m, 5H), 3.42 (dd, 1H), 3.16-3.06 (m, 2H), 2.96-2.84 (m, 3H), 2.50 (m, 1H), 2.02 (m, 1H), 1.58 (m, 1H), 1.40 (dd, 1H), 0.94 (d, 3H), 0.89 (d, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  16.2; MS (ESI) 671 (M-H).

**Example Section B**

There is no Section B in this application.



### Example Section C

#### Example 1

Diphenyl phosphonate 31: To a solution of phosphonic acid 30 (11 g, 16.4 mmol) and phenol (11 g, 117 mmol) in pyridine (100 mL) was added 1, 3-dicyclohexylcarbodiimide (13.5 g, 65.5 mmol). The solution was stirred at room temperature for 5 min and then at 70°C for 2h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (100 mL) and filtered. The filtrate was evaporated under reduced pressure to remove pyridine. The residue was dissolved in ethyl acetate (250 mL) and acidified to pH = 4 by addition of HCl (0.5 N) at 0°C. The mixture was stirred at 0°C for 0.5 h, filtered and the organic phase was separated and washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified on silica gel to give diphenyl phosphonate 31 (9 g, 67%) as a solid. <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 12.5.

#### Example 2

Monophenyl phosphonate 32: To a solution of diphenylphosphonate 31 (9.0 g, 10.9 mmol) in acetonitrile (400 mL) was added NaOH (1N, 27 mL) at 0°C. The reaction mixture was stirred at 0°C for 1 h, and then treated with Dowex (50WX8-200, 12 g). The mixture was stirred for 0.5 h at 0°C, and then filtered. The filtrate was concentrated under reduced pressure and co-evaporated with toluene. The residue was dissolved in ethyl acetate and hexane was added to precipitate out the monophenyl phosphonate 32 (8.1 g, 100%). <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 18.3.

#### Example 3

Monoamidate 33a (R<sub>1</sub> = Me, R<sub>2</sub> = n-Bu): To a flask charged with monophenyl phosphonate 32 (4.0 g, 5.35 mmol), was added L-alanine n-butyl ester hydrochloride (4.0 g, 22 mmol), 1, 3-dicyclohexylcarbodiimide (6.6 g, 32 mmol), and finally pyridine (30 mL) under nitrogen. The resultant mixture was stirred at 60 – 70°C for 1 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and HCl (0.2 N) and the organic layer was separated. The ethyl acetate phase was washed with water, saturated NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified on silica gel (pre-treated with 10% MeOH / CH<sub>3</sub>CO<sub>2</sub>Et, eluting with 40% CH<sub>2</sub>Cl<sub>2</sub> / CH<sub>3</sub>CO<sub>2</sub>Et and CH<sub>3</sub>CO<sub>2</sub>Et) to give two isomers of 33a in a total yield of 51%.

- Isomer A (1.1 g): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.88 (m, 9H), 1.3 (m, 2H), 1.35 (d, J = 7 Hz, 3H), 1.55 (m, 2H), 1.55-1.7 (m, 2H), 1.8 (m, 1H), 2.7-3.2 (m, 7H), 3.65-4.1 (m, 9H), 3.85 (s, 3H), 4.2 (m, 1H), 4.3 (d, J = 9.6 Hz, 2H), 5.0 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.0 (d, J = 8.7 Hz, 2H), 7.1-7.3 (m, 7H), 7.7 (d, J = 8.7 Hz, 2H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 20.5.
- 5 Isomer B (1.3 g) <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.88 (m, 9H), 1.3 (m, 2H), 1.35 (d, J = 7 Hz, 3H), 1.55 (m, 2H), 1.55-1.7 (m, 2H), 1.8 (m, 1H), 2.7-3.2 (m, 7H), 3.65-4.1 (m, 9H), 3.85 (s, 3H), 4.2-4.35 (m, 3H), 5.0 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.0 (d, J = 8.7 Hz, 2H), 7.1-7.3 (m, 7H), 7.7 (d, J = 8.7 Hz, 2H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 19.4.

10 Example 4

- Monoamidate **33b** (R<sub>1</sub> = Me, R<sub>2</sub> = i-Pr) was synthesized in the same manner as **33a** in 77% yield. Isomer A : <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.9 (2d, J = 6.3Hz, 6H), 1.2 (d, J = 7 Hz, 6H), 1.38 (d, J = 7 Hz, 3H), 1.55-1.9 (m, 3H), 2.7-3.2 (m, 7H), 3.65-4.1 (m, 8H), 3.85 (s, 3H), 4.2 (m, 1H), 4.3 (d, J = 9.6 Hz, 2H), 5.0 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.0 (d, J = 8.7 Hz, 2H), 7.1-7.3 (m, 7H), 7.7 (d, J = 8.7 Hz, 2H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 20.4.
- 15 Isomer B: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.9 (2d, J = 6.3Hz, 6H), 1.2 (d, J = 7 Hz, 6H), 1.38 (d, J = 7 Hz, 3H), 1.55-1.9 (m, 3H), 2.7-3.2 (m, 7H), 3.65-4.1 (m, 8H), 3.85 (s, 3H), 4.2 (m, 1H), 4.3 (d, J = 9.6 Hz, 2H), 5.0 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.0 (d, J = 8.7 Hz, 2H), 7.1-7.3 (m, 7H), 7.7 (d, J = 8.7 Hz, 2H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 19.5.

## Example Section D

### Example 1

Cyclic Anhydride 1 (6.57 g, 51.3 mmol) was treated according to the procedure of Brown et al., J. Amer. Chem. Soc. 1955, 77, 1089 -1091 to afford amino alcohol 3 (2.00g, 33%). *for intermediate 2* :  $^1\text{H NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  2.40 (s, 2H), 1.20 (s, 6H).

### Example 2

Amino alcohol 3 (2.0 g, 17 mmol) was stirred in 30 mL 1:1 THF: water. Sodium Bicarbonate (7.2 g, 86 mmol) was added, followed by Boc Anhydride (4.1 g, 19 mmol). The reaction was stirred for 1 hour, at which time TLC in 5% methanol/DCM with ninhydrin stain showed completion. The reaction was partitioned between water and ethyl acetate. The organic layer was dried and concentrated, and the resulting mixture was chromatographed on silica in 1:1 hexane: ethyl acetate to afford two fractions, "upper" and "lower" each having the correct mass. By NMR the correct product 4 was "lower" (0.56 g, 14%)  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  3.7 (t, 2H), 3.0 (d, 2H), 1.45 (t, 2H) 1.4 (s, 9H), 0.85 (s, 6H), MS (ESI): 240 (M + 23).

### Example 3

Sodium Hydride (60% emulsion in oil) was added to a solution of the alcohol 4 (1.1g, 5.2 mmol) in dry DMF in a 3-neck flask under dry nitrogen. Shortly afterward triflate 35 (2.4 g, 5.7 mmol) was added with stirring for 1.5 hrs. Mass spectrometry showed the presence of the starting material (240, M+23), thus 100 mg more 60% sodium hydride emulsion as well as ~1 g more triflate were added with an additional hour of stirring. The reaction was quenched by the addition of saturated  $\text{NaHCO}_3$  then partitioned between ethyl acetate and water. The organic layer was dried with brine and  $\text{MgSO}_4$  and eluted on silica with 1:1 hexane:ethyl acetate to afford 5 (0.445 g, 15%). NMR showed some contamination with alcohol 4 starting material.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.28 (s, 10H), 5.00 (m, 4H), 3.70 (t, 2H), 2.94, (d, 2H), 1.44 (t, 2H), 1.40 (s, 9H), 0.83 (s, 6H) MS (ESI): 514 (M+23).

### Example 4

Phosphonate ester 5 (0.445 g, 0.906 mmol) was stirred with with 20% TFA in DCM. (5 mL) TLC showed completion in 1 hr time. The reaction was azeotroped with toluene then run on

a silica gel column with 10% methanol in DCM. Subsequently, the product was dissolved in ethyl acetate and shaken with saturated sodium bicarbonate: water (1:1), dried with brine and magnesium sulfate to afford the free amine 6 (30mg, 8.5%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.30 (s, 10H), 5.00 (m, 4H), 3.67 (d, 2H), 3.47, (t, 2H), 2.4-2.6 (brs) 1.45 (t, 2H), 0.82 (s, 6H), MS (ESI): 393 (M+1).

#### Example 5

Amine 6 (30 mg, 0.08 mmol) and epoxide 7 (21 mg, 0.08 mmol) were dissolved in 2 mL IprOH and heated to reflux for 1 hr then monitored by TLC in 10% MeOH/DCM. Added ~20 mg more epoxide 7 and continued reflux for 1 hr. Cool to room temperature, dilute with ethyl acetate, shake with water and brine, dry with magnesium sulfate. Silica gel chromatography using first 5% then 10% MeOH in EtOAc yielded amine 8 (18 mg, 36%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.30 (s, 10H), 7.20-7.14 (m, 5H), 5.25-4.91 (m, 4H), 3.83, (m, 1H), 3.71 (d, 2H) 3.64 (m, 1H), 3.54 (t, 2H), 3.02-2.61 (m, 5H), 2.65-2.36 (dd, 2H) (t, 2H), 1.30 (s, 9H) 0.93 (s, 9H) 0.83 (t, 2H) MS (ESI) 655 (M+1).

#### Example 6

Amine 8 (18 mg, 0.027 mmol) was dissolved in 1 mL DCM then acid chloride 9 (6 mg, 0.2 mmol) followed by triethylamine (0.004 mL, 0.029 mmol). The reaction was monitored by TLC. Upon completion the reaction was diluted with DCM shaken with 5% citric acid, saturated sodium bicarbonate, brine, and dried with  $\text{MgSO}_4$ . Purification on silica (1:1 Hexane:EtOAc) afforded sulfonamide 10 (10.5 mg, 46%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.69 (d, 2H), 7.30 (s, 10H), 7.24-7.18 (m, 5H), 5.00 (m, 4H), 4.73, (d, 1H), 4.19 (s, 1H) 3.81 (m, 1H), 3.80 (s, 3H), 3.71 (d, 2H), 3.57 (t, 2H), 3.11-2.95 (m, 5H) 2.75 (m, 1H) 1.25 (s, 1H), 0.90 (s, 6H) MS (ESI) 847 (M+Na<sup>+</sup>).

#### Example 7

Sulfonamide 10 (10.5 mg, 0.013 mmol) was stirred at room temperature in 20% TFA/DCM. Once Boc deprotection was complete by TLC (1:1 Hexane:EtOAc) and MS, the reaction was azeotroped with toluene. The TFA salt of the amine was dissolved in acetonitrile (0.5 mg) and to this were added carbonate 11 (4.3 mg, 0.014 mmol) followed by DMAP (4.6 mg, 0.038 mg). Stir at room temp until TLC (1:1 Hexane:EtOAc) shows completion. Solvent was evaporated and the residue was redissolved in EtOAc then shaken

with saturated  $\text{NaHCO}_3$ . The organic layer was washed with water and brine, then dried with  $\text{MgSO}_4$ . Purification on silica with Hexane: EtOAc afforded compound 12 (7.1 mg, 50%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.75 (d, 2H) 7.24-7.35 (15H) 6.98 (d, 2H), 5.62 (d, 1H) 5.04 (m, 4H) 4.98 (m, 1H) 4.03 (m, 1H), 3.85 (s, 3H), 3.61-3.91 (9H), 3.23-3.04 (5H) 2.85 (m, 1H), 2.74 (m, 1H) 1.61 (d, 2H), 1.55 (m, 1H) 1.36 (m, 1H) 0.96 (d, 6H) MS (ESI): 903 (M+23).

#### Example 8

Compound 12 (6.1 mg, 0.007 mmol) was dissolved in 1 mL 3:1 EtOH:EtOAc. Palladium catalyst (10% on C, 1mg) was added and the mixture was purged three times to vacuum with 1 atmosphere hydrogen gas using a balloon. The reaction was stirred for 2 hrs, when MS and TLC showed completion. The reaction was filtered through Celite with EtOH washing and all solvent to was evaporated to afford final compound 13 (5mg, 100%).  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  7.79 (d, 2H) 7.16-7.24 (5H) 7.09 (d, 2H) 5.58 (d, 1H) 4.92 (m, 1H) 3.97 (m, 1H), 3.92 (dd, 1H) 3.89 (s, 3H) 3.66-3.78 (8H) 3.40 (d, 1H), 3.37 (dd, 1H), 3.15 (m, 1H) 3.12 (dd, 1H) 2.96 (d, 1H), 2.87 (m, 1H), 2.74 (m, 1H) 2.53 (m, 1H) 1.70 (m, 2H), 1.53 (m, 1H) 1.32 (m, 1H) 1.04 (d, 6H) MS (ESI): 723 (M+23).

#### Example 9

Amino Alcohol 14 (2.67g, 25.9 mmol) was dissolved in THF with stirring and Boc Anhydride (6.78g, 31.1 mmol) was added. Heat and gas evolution ensued. TEA (3.97 mL, 28.5 mmol) was added and the reaction was stirred overnight. In the morning, the reaction was quenched by the addition of saturated  $\text{NaHCO}_3$ . The organic layer was separated out and shaken with water, dried with brine and  $\text{MgSO}_4$  to afford 15 which was used without further purification. (100% yield) (some contamination):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  3.76 (t, 1H) 3.20, (d, 2H), 2.97 (d, 2H), 1.44 (s, 9H), 0.85 (s, 6H).

#### Example 10

A solution of the alcohol 15 (500 mg, 2.45 mmol) in dry THF was cooled under dry  $\text{N}_2$  with stirring. To this was added n-butyl lithium (1.29 mL, 2.71 mmol) as a solution in hexane in a manner similar to that described in Tetrahedron. 1995, 51 #35, 9737-9746. Triflate 35 (1.15 g, 2.71 mmol) was added neat with a tared syringe. The reaction was stirred for four hours, then quenched with saturated  $\text{NaHCO}_3$ . The mixture was then partitioned between water and EtOAc. The organic layer was dried with brine and  $\text{MgSO}_4$ , then chromatographed on silica

in 1:1 Hexane:EtOAc to afford phosphonate 16 (445mg, 38%)  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.37 (m, 10H), 5.09 (m, 4H), 3.73-3.75 (m, 2H), 3.24 (s, 2H), 3.02 (d, 2H), 1.43 (s, 9H), 0.86 (s, 6H).

#### Example 11

- 5 Phosphonate 16 (249 mg, 0.522 mmol) was stirred in 20% TFA/DCM for 1 hr. The reaction was then azeotroped with toluene. The residue was re-dissolved in EtOAc, then shaken with water: saturated  $\text{NaHCO}_3$  (1:1). The organic layer was dried with brine and  $\text{MgSO}_4$  and solvent was removed to afford amine 17 (143 mg, 73%)  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.30 (s, 10H), 5.05-4.99 (m, 4H), 3.73 (d, 2H), 3.23 (s, 2H), 2.46 (brs, 2H), 0.80 (s, 6H)  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ ):  
10  $\delta$  23.77 (s).

#### Example 12

- Amine 17 (143 mg, 0.379 mmol) and epoxide 7 (95 mg, 0.360 mmol) were dissolved in 3 mL  $\text{iPrOH}$  and heated to  $85^\circ\text{C}$  for 1 hr. The reaction was cooled to room temperature overnight  
15 then heated to  $85^\circ\text{C}$  for 1 hr more in the morning. The reaction was then diluted with EtOAc, shaken with water, dried with brine  $\text{MgSO}_4$  and concentrated. The residue was eluted on silica in a gradient from 5% to 10% MeOH in DCM to afford compound 18 (33 mg, 14%).

#### Example 13

- 20 Mix compound 18 (33 mg, 0.051 mmol) and chlorosulfonyl compound 9 (11 mg, 0.054 mmol) in 2 mL DCM then add TEA (0.0075 mL, 0.054 mmol), stir for 5 hrs. TLC in 1:1 EtOAc: hexane shows reaction not complete. Place in freezer overnight. In the morning, take out of freezer, stir for 2 hrs, TLC shows completion. Workup done with 5% citric acid, saturated  $\text{NaHCO}_3$ , then dry with brine and  $\text{MgSO}_4$ . The reaction mixture was concentrated  
25 and chromatographed on a Monster Pipette column in 1:1 hexane: EtOAc then 7:3 hexane: EtOAc to avail compound 19 (28 mg, 67%)  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.37 (d, 2H), 7.20 (m, 15H), 6.90 (d, 2H), 5.07-4.93 (m, 4H), 4.16 (brs, 1H), 3.80 (s, 3H), 3.75-3.37 (m, 4H), 3.36 (d, 1H), 3.20-2.93 (m, 6H), 2.80- 2.75 (dd, 1H).

#### Example 14

Compound 19 (28 mg, 0.35 mmol) was stirred in 4 mL DCM with addition of 1 mL TFA. Stir for 45 minutes, at which time complete deprotection was noted by TLC as well as MS. Azeotrope with toluene. The residue was dissolved in 1 mL  $\text{CH}_3\text{CN}$ , cooled to  $0^\circ\text{C}$ . Bis-

Furan *para*-Nitro phenol carbonate 11 (12 mg, 0.038 mmol), dimethyl amino pyridine (~ 1 mg, 0.008 mmol) and diisopropylethylamine (0.018 mL, 0.103 mmol) were added. The mixture was stirred and allowed to come to room temperature and stirred until TLC in 1:1 hexane:EtOAc showed completion. The reaction mixture was concentrated and the residue  
5 was partitioned between saturated NaHCO<sub>3</sub> and EtOAc. The organic layer was dried with brine and MgSO<sub>4</sub>, then chromatographed on silica with hexane:EtOAc to afford compound 20 (20 mg, 67%). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.76 (d, 2H), 7.34–7.16 (m, 15 H), 7.07 (d, 2H), 5.56 (d, 1H), 5.09 (m, 4H), 4.87 (m, 1H), 4.01 (m, 1H), 3.91 (m, 2H), 3.87 (s, 3H), 3.86 (m, 1H), 3.69 (m, 1H), 3.67 (m, 1H) 3.60 (d, 2H) 3.28 (m, 1H) 3.25 (d, 2H), 3.32 (d, 1H), 3.13 (m, 1H),  
10 3.02 (m, 1H) 2.85 (d, 1H), 2.83 (m, 1H) 2.52 (m, 1H) 1.47 (m, 1H), 1.31 (m, 1H) 0.98 (s, 3H), 0.95 (s, 3H).

#### Example 15

Compound 20 (7 mg, 0.008 mmol) was treated in a manner identical to example 8 to afford  
15 compound 21 (5 mg, 90%) <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.80 (d, 2H), 7.25–7.16 (m, 5H), 7.09 (d, 2H), 5.58 (d, 1H), 4.92 (m, 1H), 3.99 (m, 1H), 3.92 (m, 1H), 3.88 (s, 3H), 3.86 (m, 1H), 3.77 (m, 1H), 3.75 (m, 1H), 3.73 (m, 1H), 3.71 (m, 1H) 3.71 (m, 1H), 3.68 (m, 1H), 3.57 (d, 1H), 3.41 (d, 1H), 3.36 (m, 1H), 3.29 (d, 1H), 3.25 (d, 2H), 3.18 (m, 1H), 3.12 (m, 1H), 3.01 (d, 1H) 2.86 (m, 1H), 2.53 (m, 1H) 1.50 (m, 1H), 1.33 (m, 1H), 1.02 (s, 3H), 0.99 (s,  
20 3H).

#### Example 16

Compound 15 (1.86 g, 9.20 mmol) was treated with triflate 22 in a manner identical to example 10 to afford compound 23 (0.71 g, 21.8%) <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 5.21 (brs, 1H) 4.16–  
25 4.07 (m, 4H), 3.71–3.69 (d, 2H), 3.24 (s, 2H), 1.43 (s, 9H), 1.34–1.28 (m, 6H) 0.86 (s, 6H).

#### Example 17

Compound 23 (151 mg, 0.427 mmol) was dissolved in 10 mL DCM and 1.0 mL TFA was added. The reaction was stirred until completion. The reaction was azeotroped with toluene  
30 and the residue was then dissolved in THF and treated with basic Dowex resin beads. Afterwards, the beads were filtered away and solvent was removed to avail compound 24 (100 mg, 92%) <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 4.15–4.05 (m, 4H), 3.72–3.69 (d, 2H), 3.27 (s, 2H), 1.30–1.26 (m, 6H) 0.81 (s, 6H).

Example 18

Compound 24 (100 mg, 0.395 mmol) was treated in a manner identical to example 12 to afford compound 25 (123 mg, 60%). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.26–7.13 (m, 5H), 4.48–4.83 (d, 1H)  
5 4.17–4.06 (m, 4H), 3.75 (d, 2H) 3.56 (brs, 1H), 3.33 (s, 2H), 2.93–2.69 (m, 4H), 2.44–2.55 (dd, 2H) 1.32 (m, 6H), 0.916 (s, 6H).

Example 19

Compound 25 (88 mg, 0.171 mmol) was treated in a manner identical to example 13 to afford  
10 compound 26 (65 mg, 55%) <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.26–7.13 (m, 5H), 4.48–4.83 (d, 1H) 4.17–4.06 (m, 4H), 3.75 (d, 2H) 3.56 (brs, 1H), 3.33 (s, 2H), 2.93–2.69 (m, 4H), 2.44–2.55 (dd, 2H) 1.32 (m, 6H), 0.916 (s, 6H).

Example 20

15 Compound 26 (65 mg, 0.171 mmol) was treated in a manner identical to example 14 to afford compound 27 (49 mg, 70%) <sup>1</sup>H NMR:  
(CDCl<sub>3</sub>): δ 7.75 (d, 2H), 7.25–7.24 (m, 4 H), 7.18 (m, 1H) 6.99 (d, 2H), 5.63 (d, 1H), 5.01 (m, 1H), 4.16 (m, 4H), 3.94 (m, 1H), 3.88 (m, 1H), 3.88 (s, 3H), 3.84 (m, 1H), 3.81 (m, 1H), 3.74 (m, 2H), ), 3.70 (m, 1H), 3.69 (m, 1H) 3.43 (m, 1H), 3.24 (m, 1H), 3.22 (m, 2H) 3.21 (m,  
20 2H) 3.12 (m, 1H), 3.02 (m, 1H) 2.86 (m, 1H), 2.72 (m, 1H), 1.54 (m, 1H), 1.38 (m, 1H) 1.35 (m, 6H) 1.00 (s, 3H), 0.96 (s, 3H).

Example 21

Boc protected amine 28 (103 mg, 0.153 mmol) was dissolved in DCM (5 mL). The stirred  
25 solution was cooled to 0°C. BBr<sub>3</sub> as a 1.0 M solution in DCM (0.92 mL, 0.92 mmol) was added dropwise over 10 min, and the reaction was allowed to continue stirring at 0°C for 20 min. The reaction was warmed to room temperature and stirring was continued for 2 hours. The reaction was then cooled to 0°C and quenched by dropwise addition of MeOH (1 mL). The reaction mixture was evaporated and the residue suspended in methanol which was  
30 removed under reduced pressure. The procedure was repeated for EtOAc and finally toluene to afford free amine HBr salt 29 (107 mg, >100%) which was used without further purification.



Example 22

Amine HBr salt 29 (50 mg, 0.102 mmol) was suspended in 2 mL CH<sub>3</sub>CN with stirring then cooled to 0°C. DMAP (25 mg, 0.205 mmol) was added, followed by Carbonate 11. The reaction was stirred at 0°C for 1.5 hrs then allowed to warm to room temperature. The reaction was stirred overnight. A few drops Acetic acid were added to the reaction mixture, which was concentrated and re-diluted with ethyl acetate, shaken with 10% citric acid then saturated NaHCO<sub>3</sub>. The organic layer was dried with brine and MgSO<sub>4</sub> and eluted on silica to afford di-phenol 30 (16 mg, 28%) <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.61, (d, 2H), 7.01 (d, 2H), 6.87 (d, 2H), 6.62 (d, 2H), 5.55 (d, 1H), 4.93 (m, 1H), 3.92 (m, 2H), 3.79 (m, 5H), 3.35 (m, 1H), 3.07 (m, 2H), 2.88 (m, 3H), 2.41 (m, 1H), 2.00 (m, 1H), 1.54 (m, 1H), 1.31 (dd, 1H) 0.89-0.82 (dd, 6H).

Example 23

A solution of di-phenol 30 (100 mg, 0.177 mmol) was made in CH<sub>3</sub>CN that had been dried over K<sub>2</sub>CO<sub>3</sub>. To this, the triflate (0.084 mL, 0.23 mmol) was added, followed by Cs<sub>2</sub>CO<sub>3</sub> (173 mg, 0.531 mmol). The reaction was stirred for 1 hr. TLC (5% IprOH/DCM) showed 2 spots with no starting materials left. Solvent was evaporated and the residue was partitioned between EtOAc and water. The organic layer was washed with saturated NaHCO<sub>3</sub>, then dried with brine and MgSO<sub>4</sub>. The mixture was separated by column chromatography on silica with 3% IprOH in DCM. The upper spot 31 (90 mg, 46%) was confirmed to be the *bis* alkylation product. The lower spot required further purification on silica gel plates to afford a single *mono* alkylation product 32 (37 mg, 26%). The other possible alkylation product was not observed. NMR : <sup>1</sup>H NMR (CDCl<sub>3</sub>): for 31: δ 7.57 (d, 2H), 7.37 (m, 10H) 7.03 (d, 2H), 6.99 (d, 2H), 6.73 (d, 2H), 5.69 (d, 1H), 5.15-5.09 (m, 4H), 5.10 (m, 1H), 4.32 (d, 2H), 4.02 (d, 1H), 3.82 (m, 1H) 3.81 (m, 1H), 3.93-3.81 (m, 2H), 3.74 (d, 1H), 3.06 (m, 1H), 3.00 (m, 1H), 2.96 (m, 1H), 2.91 (m, 1H) 2.77 (m, 1H) 2.64 (m, 1H) 2.47 (m, 1H) 1.82 (m, 2H) 1.79 (m, 1H), 0.94-0.86 (dd, 6H) for 32: δ 7.68 (d, 2H), 7.33-7.35 (m, 20H), 7.11 (d, 2H), 6.96 (d, 2H), 6.80 (d, 2H), 5.26 (d, 1H), 5.11 (m, 8H), 5.00 (m, 1H) 4.23 (d, 2H), 4.19 (d, 2H), 3.93 (m, 1H), 3.82-3.83 (m, 3H), 3.68-3.69 (m, 2H) 3.12-2.75 (m, 7H), 1.82 (m, 1H), 1.62-1.52 (d, 2H), 0.89-0.86 (dd, 6H).

Example 24

Ref: J. Med. Chem. 1992, 35 10,1681-1701

To a solution of phosphonate 32 (100 mg, 0.119 mmol) in dry dioxane was added  $\text{Cs}_2\text{CO}_3$  (233 mg, 0.715 mmol), followed by 2-(dimethylamino) ethyl chloride hydrochloride salt (69 mg, 0.48 mmol). The reaction was stirred at room temperature and monitored by TLC. When it was determined that starting material remained, additional  $\text{Cs}_2\text{CO}_3$  (233 mg, 0.715 mmol) as well as amine salt (69 mg, 0.48 mmol) were added and the reaction was stirred overnight at 60°C. In the morning when TLC showed completion the reaction was cooled to room temperature, filtered, and concentrated. The product amine 33 (40 mg, 37%) was purified on silica. Decomposition was noted as lower spots were seen to emerge with time using 15% MeOH in DCM on silica.

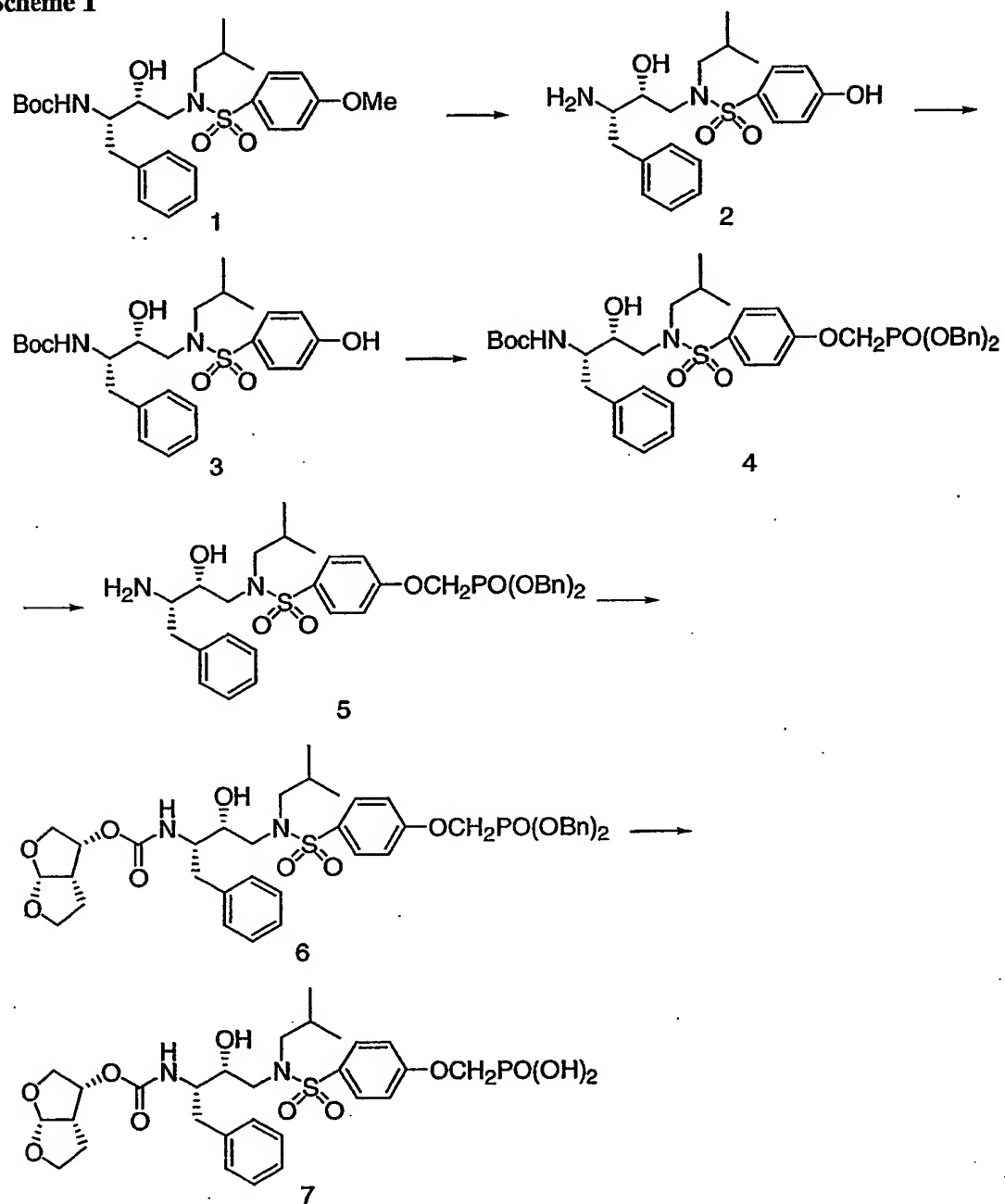
10

Example 25:

Amine 33 (19 mg, 0.021 mmol) was dissolved in 1.5 mL DCM. This solution was stirred in an icebath. Methane sulfonic acid (0.0015 mL, 0.023 mmol) was added and the reaction was stirred for 20 minutes. The reaction was warmed to room temperature and stirred for 1 hour.

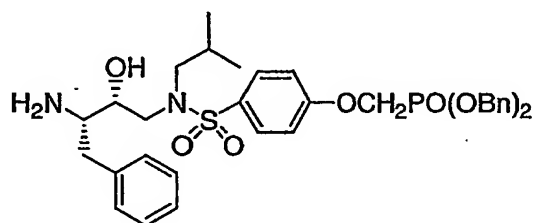
15

The product, amine mesylate salt 34 (20 mg, 95%) was precipitated out by addition of hexane.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  7.69 (d, 2H), 7.35 (m, 10H), 7.15 (m, 4H) 6.85 (m, 2H), 5.49 (d, 1H), 5.10 (m, 4H), 4.83 (m, 1H), 4.62 (d, 2H), 4.22 (m, 2H), 3.82 (m, 1H), 3.56 (m, 1H), 3.48 (m, 2H), 3.35 (m, 1H), 2.99 (m, 1H), 2.95 (m, 1H), 2.84 (s, 6H), 2.78 (m, 1H), 2.75 (m, 1H), 2.70 (m, 1H), 2.40 (m, 1H) 1.94 (m, 1H), 1.43 (m, 1H), 1.27 (m, 1H), 0.77 (dd, 6H).

**Example Section E****Scheme 1**

Example 1

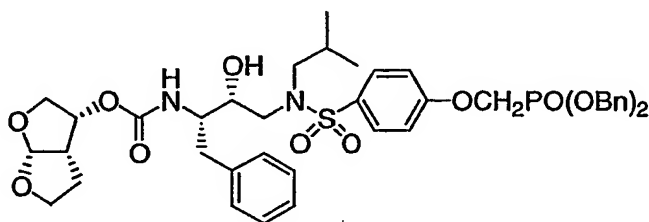
To a solution of phenol **3** (336 mg, 0.68 mmol) in THF (10 mL) was added  $\text{Cs}_2\text{CO}_3$  (717 mg, 2.2 mmol) and triflate (636 mg, 1.5 mmol) in THF (3 mL). After the reaction mixture was stirred for 30 min at room temperature, the mixture was partitioned between EtOAc and water. The organic phase was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 40-50% EtOAc/hexane) to give dibenzylphosphonate **4** (420 mg, 80%) as a colorless oil.

Example 2

10

To a solution of dibenzylphosphonate **4** (420 mg, 0.548 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) was added TFA (0.21 mL, 2.74 mmol). After the reaction mixture was stirred for 2 h at room temperature, additional TFA (0.84 mL, 11 mmol) was added and the mixture was stirred for 3 h. The reaction mixture was evaporated under reduced pressure and the residue was partitioned between EtOAc and 1M  $\text{NaHCO}_3$ . The organic phase was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure to give amine **5** (325 mg, 89%).

15

Example 3

20

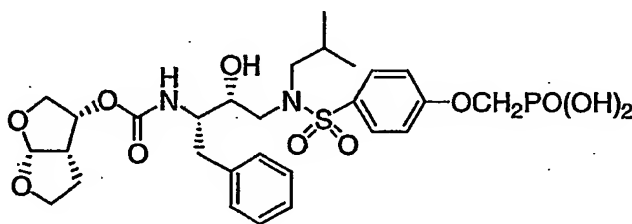
To a solution of carbonate (79 mg, 0.27 mmol), amine **5** (178 mg, 0.27 mmol), and  $\text{CH}_3\text{CN}$  (10 mL) was added DMAP (66 mg, 0.54 mmol) at  $0^\circ\text{C}$ . After the reaction mixture was warmed to room temperature and stirred for 16 hours, the mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel (eluting 60-90% EtOAc/hexane) to give a mixture of carbamate **6** and starting carbonate. The mixture was further purified by HPLC on C18 reverse phase chromatography (eluting 60%  $\text{CH}_3\text{CN}$ /water)

25

to give carbamate 6 (49 mg, 22%) as a colorless oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.68 (d, 2H), 7.22 (m, 15 H), 6.95 (d, 2H), 5.62 (d, 1H), 5.15 (dt, 4H), 5.00 (m, 2H), 4.21 (d, 2H), 3.88 (m, 4H), 3.67 (m, 3H), 3.15 (m, 2H), 2.98 (m, 3H), 2.80 (m, 2H), 1.82 (m, 1H), 1.61 (m, 1H), 0.93 (d, 3H), 0.88 (d, 3H).

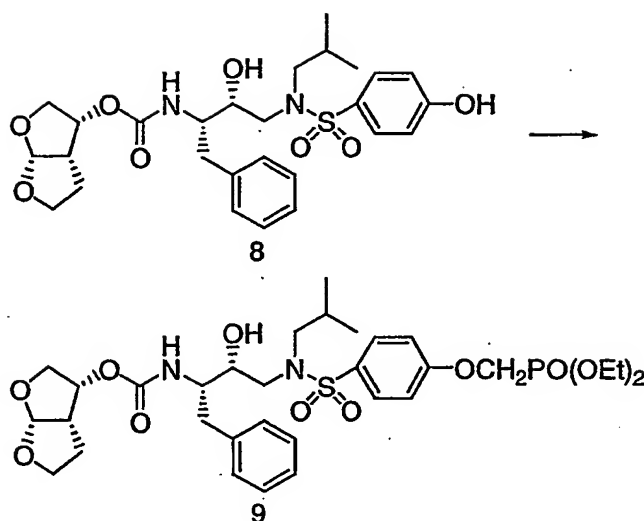
5

#### Example 4

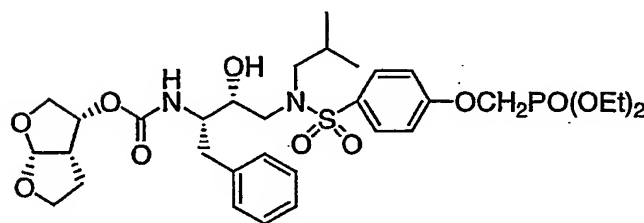


To a solution of carbamate 6 (21 mg, 0.026 mmol) in EtOH / EtOAc (2 mL/1 mL) was added 10% Pd/C (11 mg). After the reaction mixture was stirred under H<sub>2</sub> atmosphere (balloon) for 2 hours, the mixture was filtered through Celite. The filtrate was evaporated under reduced pressure to give phosphonic acid 7 (17 mg, 100%) as a colorless solid. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 7.73 (d, 2H), 7.19 (m, 5H), 7.13 (d, 2H), 5.53 (d, 1H), 4.26 (d, 2H), 3.86 (m, 1H), 3.64 (m, 5H), 3.38 (d, 1H), 3.13 (d, 1H), 3.03 (dd, 1H), 2.86 (m, 3H), 2.48 (m, 1H), 1.97 (m, 1H), 1.47 (m, 1H), 1.28 (m, 2H), 1.13 (t, 1H), 0.88 (d, 3H), 0.83 (d, 3H).

## Scheme 2



## Example 5

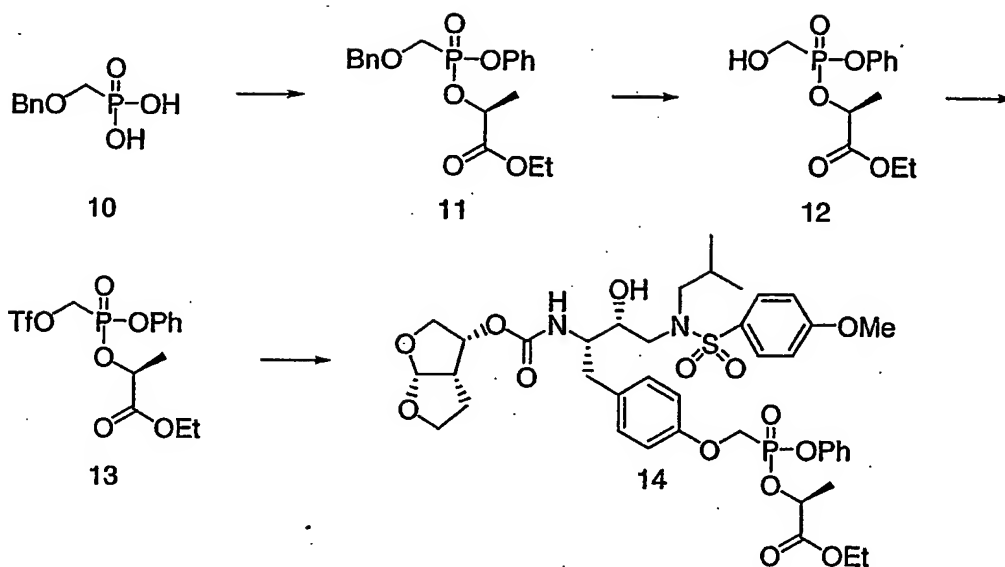


5

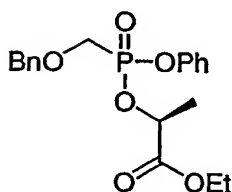
To a solution of phenol **8** (20 mg, 0.036 mmol) and triflate (22 mg, 0.073 mmol) in THF (2 mL) was added  $\text{Cs}_2\text{CO}_3$  (29 mg, 0.090 mmol). After the reaction mixture was stirred for 30 min at room temperature, the mixture was partitioned between EtOAc and water. The organic phase was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude product was purified by preparative thin layer chromatography (eluting 80% EtOAc/hexane) to give diethylphosphonate **9** (21 mg, 83%) as a colorless oil.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.73 (d, 2H), 7.25 (m, 5H), 7.07 (d, 2H), 5.64 (d, 1H), 5.01 (m, 2H), 4.25 (m, 6H), 3.88 (m, 4H), 3.70 (m, 3H), 2.97 (m, 6H), 1.70 (m, 4H), 1.38 (t, 6H), 0.92 (d, 3H), 0.88 (d, 3H).  $^{31}\text{P}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  18.1.

15

## Scheme 3

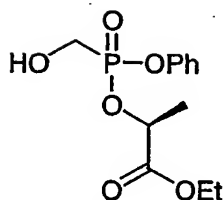


## Example 6



5

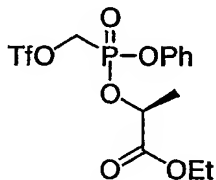
To a solution of phosphonic acid **10** (520 mg, 2.57 mmol) in  $\text{CH}_3\text{CN}$  (5 mL) was added thionyl chloride (0.75 mL, 10.3 mmol) and heated to  $70^\circ\text{C}$  in an oil bath. After the reaction mixture was stirred for 2 h at  $70^\circ\text{C}$ , the mixture was concentrated and azeotroped with toluene. To a solution of the crude chloridate in toluene (5 mL) was added tetrazole (18 mg, 0.26 mmol) at  $0^\circ\text{C}$ . To this mixture was added phenol (121 mg, 1.28 mmol) and triethylamine (0.18 mL, 1.28 mmol) in toluene (3 mL) at  $0^\circ\text{C}$ . After the reaction mixture was warmed to room temperature and stirred for 2 h, ethyl lactate (0.29 mL, 2.57 mmol) and triethylamine (0.36 mL, 2.57 mmol) in toluene (2.5 mL) were added. The reaction mixture was stirred for 16 hours at room temperature, at which time the mixture was partitioned between EtOAc and sat.  $\text{NH}_4\text{Cl}$ . The organic phase was washed with sat.  $\text{NH}_4\text{Cl}$ , 1M  $\text{NaHCO}_3$ , and brine, then dried over  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 20-40% EtOAc/hexane) to give two diastereomers of phosphonate **11** (66 mg, 109 mg, 18% total) as colorless oils.

Example 7A

To a solution of phosphonate **11** isomer A (66 mg, 0.174 mmol) in EtOH (2 mL) was added  
5 10% Pd/C (13 mg). After the reaction mixture was stirred under H<sub>2</sub> atmosphere (balloon) for 6 h, the mixture was filtered through Celite. The filtrate was evaporated under reduced pressure to give alcohol **12** isomer A (49 mg, 98%) as a colorless oil.

Example 7B

10 To a solution of phosphonate **11** isomer B (110 mg, 0.291 mmol) in EtOH (3 mL) was added 10% Pd/C (22 mg). After the reaction mixture was stirred under H<sub>2</sub> atmosphere (balloon) for 6 h, it was filtered through Celite. The filtrate was evaporated under reduced pressure to give alcohol **12** isomer B (80 mg, 95%) as a colorless oil.

15 Example 8A

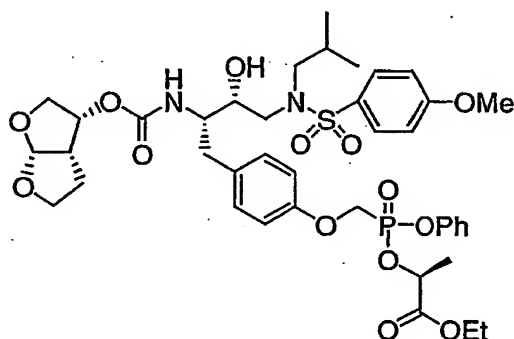
To a solution of alcohol **12** isomer A (48 mg, 0.167 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added 2,6-lutidine (0.03 mL, 0.250 mmol) and trifluoromethanesulfonic anhydride (0.04 mL, 0.217  
20 mmol) at -40°C (dry ice-CH<sub>3</sub>CN bath). After the reaction mixture was stirred for 15 min at -40°C, the mixture was warmed to 0°C and partitioned between Et<sub>2</sub>O and 1M H<sub>3</sub>PO<sub>4</sub>. The organic phase was washed with 1M H<sub>3</sub>PO<sub>4</sub> (3 times), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure to give triflate **13** isomer A (70 mg, 100%) as a pale yellow oil.

25

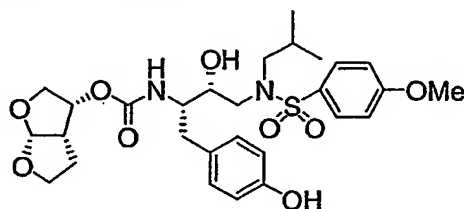


Example 8B

To a solution of alcohol **12** isomer B (80 mg, 0.278 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 mL) was added 2,6-lutidine (0.05 mL, 0.417 mmol) and trifluoromethanesulfonic anhydride (0.06 mL, 0.361 mmol) at  $-40^\circ\text{C}$  (dry ice- $\text{CH}_3\text{CN}$  bath). After the reaction mixture was stirred for 15 min at  $-40^\circ\text{C}$ , the mixture was warmed to  $0^\circ\text{C}$  and partitioned between  $\text{Et}_2\text{O}$  and 1M  $\text{H}_3\text{PO}_4$ . The organic phase was washed with 1M  $\text{H}_3\text{PO}_4$  (3 times), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure to give triflate **13** isomer B (115 mg, 98%) as a pale yellow oil.

10 Example 9A

To a solution of phenol (64 mg, 0.111 mmol):



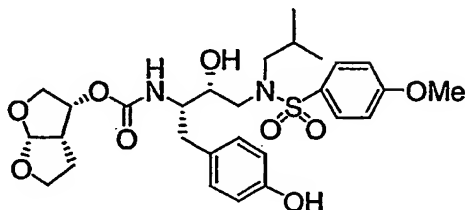
15 and triflate **13** isomer A (70 mg, 0.167 mmol) in THF (2 mL) was added  $\text{Cs}_2\text{CO}_3$  (72 mg, 0.222 mmol). After the reaction mixture was stirred for 30 min at room temperature, the mixture was partitioned between  $\text{EtOAc}$  and water. The organic phase was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 60-80%  $\text{EtOAc}$ /hexane) to give a mixture. The mixture was further purified by HPLC on C18 reverse phase chromatography (eluting 55%  $\text{CH}_3\text{CN}$ /water) to give phosphonate **14** isomer A (30 mg, 32%) as a colorless solid.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.71 (d, 2H), 7.26 (m, 6H), 7.00 (m, 5H), 5.65 (d, 1H), 5.14 (m, 1H), 5.00 (m, 2H), 4.54 (dd, 1H), 4.44 (dd, 1H), 4.17 (m, 2H), 3.96 (dd, 1H), 3.86 (m, 5H), 3.72

(m, 3H), 3.14 (m, 1H), 2.97 (m, 4H), 2.79 (m, 2H), 1.83 (m, 1H), 1.62 (m, 3H), 1.50 (d, 3H), 1.25 (m, 3H), 0.93 (d, 3H), 0.88 (d, 3H).  $^{31}\text{P}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  17.4.

### Example 9B

5

To a solution of phenol (106 mg, 0.183 mmol):



and triflate 13 isomer B (115 mg, 0.274 mmol) in THF (2 mL) was added  $\text{Cs}_2\text{CO}_3$  (119 mg, 0.366 mmol). After the reaction mixture was stirred for 30 min at room temperature, the  
10 mixture was partitioned between EtOAc and water. The organic phase was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 60-80% EtOAc/hexane) to give a mixture. The mixture was further purified by HPLC on C18 reverse phase chromatography (eluting 55%  $\text{CH}_3\text{CN}$ /water) to give phosphonate 14 isomer B (28 mg, 18%) as a colorless solid.  $^1\text{H}$  NMR  
15 (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.71 (d, 2H), 7.26 (m, 6H), 6.94 (m, 5H), 5.66 (d, 1H), 5.17 (m, 1H), 4.99 (m, 2H), 4.55 (m, 1H), 4.42 (m, 1H), 4.16 (m, 2H), 3.97 (m, 1H), 3.85 (m, 5H), 3.72 (m, 3H), 3.13 (m, 1H), 2.97 (m, 4H), 2.80 (m, 2H), 1.83 (m, 1H), 1.60 (m, 6H), 1.22 (m, 3H), 0.93 (d, 3H), 0.88 (d, 3H).  $^{31}\text{P}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  15.3.

20

### Resolution of Compound 14 Diastereomers

Analysis was performed on an analytical Alltech Econosil column, conditions described below, with a total of about 0.5 mg 14 injected onto the column. This lot was a mixture of major and minor diastereomers where the lactate ester carbon is a mix of R and S  
25 configurations. Up to 2 mg could be resolved on the analytical column. Larger scale injections (up to 50 mg 14) were performed on an Alltech Econosil semi-preparative column, conditions described below.

The isolated diastereomer fractions were stripped to dryness on a rotary evaporator under  
30 house vacuum, followed by a final high vacuum strip on a vacuum pump. The

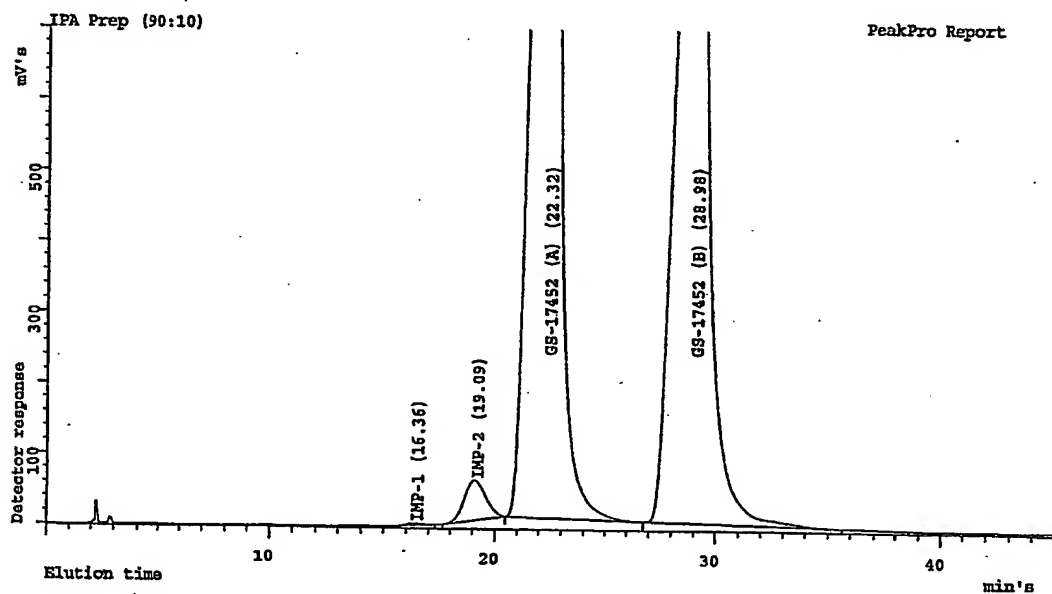
chromatographic solvents were displaced by two portions of dichloromethane before the final high vacuum strip to aid in removal of trace solvents, and to yield a friable foam.

5 The bulk of the diastereomer resolution was performed with *n*-heptane substituted for hexanes for safety considerations.

Sample Dissolution: While a fairly polar solvent mixture is described below, the sample may be dissolved in mobile phase with a minimal quantity of ethyl alcohol added to dissolve the sample.

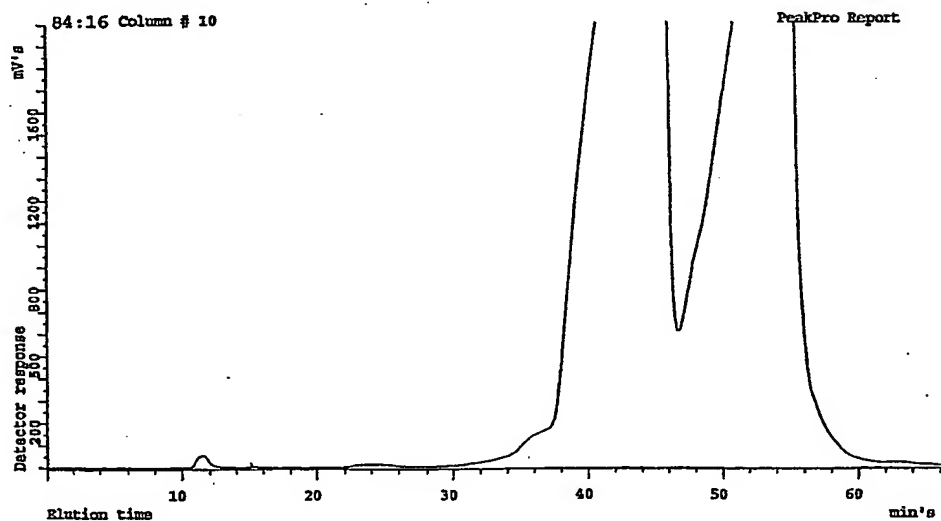
10

Analytical Column, 0.45 mg Injection, Hexanes - IPA (90:10)



**HPLC CONDITIONS**

Column : Alltech Econosil, 5  $\mu$ m, 4.6 x 250 mm  
Mobile Phase : Hexanes – Isopropyl Alcohol (90:10)  
Flow Rate : 1.5 mL/min  
Run Time : 50 min  
Detection : UV at 242 nm  
Temperature : Ambient  
Injection Size : 100  $\mu$ L  
Sample Prep. : ~ 5 mg/mL, dissolved in hexanes –  
ethyl alcohol (75:25)  
Retention Times : 14 ~ 22 min  
: 14 ~ 29 min  
: Less Polar Impurity ~ 19 min

**Semi-Preparative Column, 50 mg Injection, *n*-Heptane – IPA (84:16)**

**HPLC CONDITIONS**

Column : Alltech Econosil, 10  $\mu$ m, 22 x 250 mm  
Mobile Phase : *n*-Heptane – Isopropyl Alcohol (84:16)  
Flow Rate : 10 mL/min  
Run Time : 65 min  
Detection : UV at 257 nm  
Temperature : Ambient  
Injection Size : ~50 mg  
Dissolution : 2 mL mobile phase plus ~ 0.75 mL ethyl alcohol  
Retention Times : 14 ~ 41 min  
: 14 ~ 54 min  
: Less Polar Impurity ~ Not resolved

## Example Section F

### Example 1

Phosphonic acid 2: To a solution of compound 1 (A. Flohr et al, J. Med. Chem., 42, 12, 1999; 2633-2640) (4.45 g, 17 mmol) in  $\text{CH}_2\text{Cl}_2$  (50 mL) at room temperature was added  
5 bromotrimethylsilane (1.16 mL, 98.6 mmol). The solution was stirred for 19 h. The volatiles were evaporated under reduced pressure to give the oily phosphonic acid 2 (3.44 g, 100%).  
 $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.30 (m, 5H), 4.61 (s, 2 H), 3.69 (d, 2H).

### 10 Example 2

Compound 3: To a solution of phosphonic acid 2 (0.67 g, 3.3 mmol) in  $\text{CH}_3\text{CN}$  (5 mL) was added thionyl chloride (1 mL, 13.7 mmol) and the solution was heated at 70°C for 2.5 h. The volatiles were evaporated under reduced pressure and dried in vacuo to afford an oily  
phophonyl dichloride. The crude chloride intermediate was dissolved in  $\text{CH}_2\text{Cl}_2$  (20 mL) and  
15 cooled in an ice/water bath. Ethyl lactate (1.5 mL, 13.2 mmol) and triethyl amine (1.8 mL, 13.2 mmol) were added dropwise. The mixture was stirred for 4 h at room temperature and diluted with more  $\text{CH}_2\text{Cl}_2$  (100 mL). The organic solution was washed with 0.1N HCl, saturated aqueous  $\text{NaHCO}_3$ , and brine, dried ( $\text{MgSO}_4$ ) filtered and evaporated under reduced pressure. The crude product was chromatographed on silica gel to afford oily compound 3  
20 (0.548 g, 41%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.30 (m, 5H), 5.00-5.20 (m, 2H), 4.65 (m, 2H), 4.20 (m, 4H), 3.90 (d, 2H), 1.52 (t, 6H), 1.20 (t, 6H).

### Example 3

Alcohol 4: A solution of compound 3 (0.54 g, 1.34 mmol) in EtOH (15 mL) was treated with  
25 10% Pd/C (0.1 g) under  $\text{H}_2$  (100 psi) for 4 h. The mixture was filtered and the filtrate was treated with fresh 10% PD/C (0.1 g) under  $\text{H}_2$  (1 atmosphere) for 18 h. The mixture was filtered and the filtrate was evaporated to afford alcohol 4 (0.395 g, 94%) as an oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  4.90-5.17 (m, 2H), 4.65 (q, 2H), 4.22 (m, 4H), 4.01 (m, 2H), 1.55 (t, 6H), 1.21 (t, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  22.8.

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### Example 4

Triflate 5: To a solution of alcohol 4 (122.8 mg, 0.393 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) at -40°C were added 2,6-lutidine (0.069 mL, 0.59 mmol) and trifluoromethansulfonic anhydride

(0.086 mL, 0.51 mmol). Stirring was continued at 0°C for 2 h. and the mixture partitioned in CH<sub>2</sub>Cl<sub>2</sub> and saturated NaHCO<sub>3</sub>. The organic layer was washed with 0.1N HCl, saturated NaCl, dried (MgSO<sub>4</sub>), filtered and evaporated under reduced pressure. The crude product 5 (150 mg, 87%) was used for the next step without further purification. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 5.0-5.20 (m, 2H), 4.93 (d, 2H), 4.22 (m, 4H), 1.59 (m, 6H), 1.29 (t, 6H).

#### Example 5

Phosphonate 6: A solution of phenol 8 (see Scheme Section A, Scheme 1 and 2) (32 mg, 0.055 mmol) and triflate 5 (50 mg, 0.11 mmol) in THF (1.5 mL) at room temperature was treated with Cs<sub>2</sub>CO<sub>3</sub> (45.6 mg, 0.14 mmol). The mixture was stirred for 2.5 h and partitioned in EtOAc and saturated NaHCO<sub>3</sub>. The organic layer was washed with 0.1N HCl, saturated NaCl, dried (MgSO<sub>4</sub>), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (30-70% EtOAc/hexane) affording the phosphonate 6 (41 mg, 84%) as a solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.71 (d, 2H), 7.13 (d, 2H), 7.00 (d, 2H), 6.90 (d, 2H), 5.65 (d, 1H), 4.90-5.22 (m, 3H), 4.40 (m, 2H), 4.20 (m, 4H), 3.90 (s, 3H), 3.65-4.00 (m, 5H), 2.70-3.20 (m, 6H), 1.52-1.87 (m, 12H), 1.25 (m, 6H), 0.85-0.90 (m, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 20.0.

#### Example 6

Compound 7: To a solution of phosphonic acid 2 (0.48 g, 2.37 mmol) in CH<sub>3</sub>CN (4 mL) was added thionyl chloride (0.65 mL, 9.48 mmol) and the solution was heated at 70°C for 2.5 h. The volatiles were evaporated under reduced pressure and dried in vacuo to afford an oily phosphonyl dichloride. The crude chloride intermediate was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and cooled in an ice/water bath. Ethyl glycolate (0.9 mL, 9.5 mmol) and triethyl amine (1.3 mL, 9.5 mmol) were added dropwise. The mixture was stirred for 2 h at room temperature and diluted with more CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The organic solution was washed with 0.1N HCl, saturated aqueous NaHCO<sub>3</sub>, and saturated NaCl, dried (MgSO<sub>4</sub>) filtered and concentrated under reduced pressure. The crude product was chromatographed on silica gel to afford oily compound 7 (0.223 g, 27%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.30 (m, 5H), 4.65 (m, 6H), 4.25 (q, 4H), 3.96 (d, 2H), 1.27 (t, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 24.0.

#### Example 7

Alcohol 8: A solution of compound 7 (0.22 g, 0.65 mmol) in EtOH (8 mL) was treated with 10% Pd/C (0.04 g) under H<sub>2</sub> (1 atmosphere) for 4 h. The mixture was filtered and the filtrate was evaporated to afford alcohol 8 (0.156 g, 96%) as an oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.66 (m, 4H), 4.23 (q, 4H), 4.06 (d, 2H), 1.55 (t, 6H), 1.26 (t, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 26.8.

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#### Example 8

Triflate 9: To a solution of alcohol 8 (156 mg, 0.62 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) at -40°C were added 2,6-lutidine (0.11 mL, 0.93 mmol) and trifluoromethanesulfonic anhydride (0.136 mL, 0.8 mmol). Stirring was continued at 0°C for 2 h. and the mixture partitioned in CH<sub>2</sub>Cl<sub>2</sub> and saturated NaHCO<sub>3</sub>. The organic layer was washed with 0.1N HCl, saturated NaCl, dried (MgSO<sub>4</sub>), filtered and evaporated under reduced pressure. The crude product 9 (210 mg, 88%) was used for the next step without further purification. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.90 (d, 2H), 4.76 (d, 4H), 4.27 (q, 4H), 1.30 (t, 6H).

#### 15 Example 9

Phosphonate 10: A solution of phenol 8 (30 mg, 0.052 mmol) and triflate 9 (30 mg, 0.078 mmol) in THF (1.5 mL) at room temperature was treated with Cs<sub>2</sub>CO<sub>3</sub> (34 mg, 0.1 mmol). The mixture was stirred for 2.5 h and partitioned in EtOAc and saturated NaHCO<sub>3</sub>. The organic layer was washed with 0.1N HCl, saturated NaCl, dried (MgSO<sub>4</sub>), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (30-70% EtOAc/hexane) affording the unreacted phenol (xx) (12 mg, 40%) and the phosphonate 10 (16.6 mg, 38%) as a solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.71 (d, 2H), 7.13 (d, 2H), 7.00 (d, 2H), 6.90 (d, 2H), 5.65 (d, 1H), 5.00 (m, 2H), 4.75 (m, 4H), 4.48 (d, 2H), 4.23 (q, 4H), 3.90 (s, 3H), 3.65-4.00 (m, 5H), 2.70-3.20 (m, 6H), 2.23 (b.s., 2H), 1.52-1.87 (m, 4H), 1.25 (t, 6H), 0.85-0.90 (m, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 22.0.

25

#### Example 10

Compound 11: To a solution of phosphonic acid 2 (0.512 g, 2.533 mmol) in CH<sub>3</sub>CN (5 mL) was added thionyl chloride (0.74 mL, 10 mmol) and the solution was heated at 70°C for 2.5 h. The volatiles were evaporated under reduced pressure and dried in vacuo to afford an oily phosphoryl dichloride. The crude chloride intermediate was dissolved in toluene (8 mL) and cooled in an ice/water bath. A catalytic amount of tetrazol (16 mg, 0.21 mmol) was added followed by the addition of a solution of triethylamine (0.35 mL, 2.53 mmol) and phenol (238

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mg, 2.53 mmol) in toluene (5 mL). The mixture was stirred at room temperature for 3 h. A solution of ethyl glycolate (0.36 mL, 3.8 mmol) and triethyl amine (0.53 mL, 3.8 mmol) in toluene (3 mL) was added dropwise. The mixture was stirred for 18 h at room temperature and partitioned in EtOAc and 0.1N HCl. The organic solution was washed with saturated aqueous NaHCO<sub>3</sub>, and saturated NaCl, dried (MgSO<sub>4</sub>) filtered and concentrated under reduced pressure. The crude product was chromatographed on silica gel to afford diphenyl phosphonate as a byproduct (130 mg) and compound 11 (0.16 g, 18%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.15-7.40 (m, 10H), 4.58-4.83 (m, 4H), 4.22 (q, 2H), 4.04 (dd, 2H), 1.24 (t, 3H).

#### 10 Example 11

Alcohol 12: A solution of compound 11 (0.16 g, 0.44 mmol) in EtOH (5 mL) was treated with 10% Pd/C (0.036 g) under H<sub>2</sub> (1 atmosphere) for 22 h. The mixture was filtered and the filtrate was evaporated to afford alcohol 12 (0.112 g, 93%) as an oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.15-7.36 (m, 5H), 4.81 (dd, 1H), 4.55 (dd, 1H), 4.22 (q, 2H), 4.12 (m, 2H), 3.78 (b.s., 1H), 1.26 (t, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 22.9

#### Example 12

Triflate 13: To a solution of alcohol 12 (112 mg, 0.41 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) at -40°C were added 2,6-lutidine (0.072 mL, 0.62 mmol) and trifluoromethanesulfonic anhydride (0.09 mL, 0.53 mmol). Stirring was continued at 0°C for 3 h. and the mixture partitioned in CH<sub>2</sub>Cl<sub>2</sub> and saturated NaHCO<sub>3</sub>. The organic layer was washed with 0.1N HCl, saturated NaCl, dried (MgSO<sub>4</sub>), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (30% EtOAc/hexane) affording triflate 13 (106 mg, 64%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.36 (m, 2H), 7.25 (m, 3H), 4.80-5.10 (m, 3H), 4.60 (dd, 1H), 4.27 (q, 2H), 1.28 (t, 3H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 11.1

#### Example 13

Phosphonate 14: A solution of phenol 8 (32 mg, 0.052 mmol) and triflate 13 (32 mg, 0.079 mmol) in CH<sub>3</sub>CN (1.5 mL) at room temperature was treated with Cs<sub>2</sub>CO<sub>3</sub> (34 mg, 0.1 mmol). The mixture was stirred for 1 h and partitioned in EtOAc and saturated NaHCO<sub>3</sub>. The organic layer was washed with saturated NaCl, dried (MgSO<sub>4</sub>), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (70%

EtOAc/hexane) affording phosphonate 14 (18 mg, 40%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71 (d, 2H), 6.75-7.35 (m, 11H), 5.65 (d, 1H), 5.00 (m, 2H), 4.50-4.88 (m, 3H), 4.20 (q, 2H), 3.84 (s, 3H), 3.65-4.00 (m, 5H), 2.70-3.20 (m, 6H), 1.52-1.87 (m, 6H), 1.25 (t, 3H), 0.85-0.90 (m, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.9, 17.7.

5

#### Example 14

Piperidine 16: A solution of compound 15 (3.1 g, 3.673 mmol) in MeOH (100 mL) was treated with 10% Pd/C (0.35 g) under  $\text{H}_2$  (1 atmosphere) for 18 h. The mixture was filtered and the filtrate was evaporated to afford phenol 16 (2 g, 88%).  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.76 (d, 2H), 7.08 (d, 2H), 7.04 (d, 2H), 6.65 (d, 2H), 5.59 (d, 1H), 4.95 (m, 1H), 3.98 (s, 3H), 3.65-4.00 (m, 5H), 3.30-3.50 (m, 3H), 2.80-3.26 (m, 5H), 2.40-2.70 (m, 3H), 1.35-2.00 (m, 7H), 1.16 (m, 2H); MS (ESI) 620 (M+H).

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#### Example 15

Formamide 17: Piperidine 16 obtained above (193 mg, 0.3118 mmol) in DMF (4 mL) was treated with formic acid (0.035 mL, 0.936 mmol), triethylamine (0.173 mL, 1.25 mmol) and EDCI (179 mg, 0.936 mmol) at room temperature. The mixture was stirred for 18 h and partitioned in EtOAc and saturated  $\text{NaHCO}_3$ . The organic layer was washed with saturated NaCl, dried ( $\text{MgSO}_4$ ), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (EtOAc/hexane) affording formamide 17 (162 mg, 80%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.96 (s, 1H), 7.68 (d, 2H), 7.04 (d, 2H), 6.97 (d, 2H), 6.76 (d, 2H), 5.63 (d, 1H), 5.37 (bs, 1H), 5.04 (m, 1H), 4.36 (m, 1H), 3.93 (s, 3H), 3.52-3.95 (m, 7H), 2.70-3.20 (m, 8H), 1.48-2.00 (m, 7H), 1.02 (m, 2H).

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#### Example 16

Dibenzyl phosphonate 18: A solution of phenol 17 (123 mg, 0.19 mmol) and dibenzyl trifluoromethanesulfonyloxymethanphosphonate YY (120 mg, 0.28 mmol) in  $\text{CH}_3\text{CN}$  (1.5 mL) at room temperature was treated  $\text{Cs}_2\text{CO}_3$  (124 mg, 0.38 mmol). The mixture was stirred for 3 h and partitioned in  $\text{CH}_2\text{Cl}_2$  and saturated  $\text{NaHCO}_3$ . The organic layer was washed with 0.1N HCl, saturated NaCl, dried ( $\text{MgSO}_4$ ), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (10% MeOH/ $\text{CH}_2\text{Cl}_2$ ) affording phosphonate 18 (154 mg, 88%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.96 (s, 1H), 7.68 (d, 2H), 7.35 (m, 10H), 7.10 (d, 2H), 6.97 (d, 2H), 6.80 (d, 2H), 5.63 (d, 1H), 4.96-5.24 (m, 6H), 4.37

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(m, 1H), 4.20 (d, 2H), 3.84 (s, 3H), 3.52-3.95 (m, 7H), 2.55-3.20 (m, 8H), 1.48-2.00 (m, 7H), 1.02 (m, 2H).  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.3.

#### Example 17

5 Phosphonic acid 19: A solution of phosphonate 18 (24 mg, 0.026 mmol) in MeOH (3 mL) was treated with 10% Pd/C (5 mg) under  $\text{H}_2$  (1 atmosphere) for 4 h. The mixture was filtered and the filtrate was evaporated to afford phosphonic acid 19 as a solid (18 mg, 93%).  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  8.00 (s, 1H), 7.67 (d, 2H), 7.18 (d, 2H), 7.09 (d, 2H), 6.90 (d, 2H), 5.60 (d, 1H), 4.30 (m, 1H), 4.16 (d, 2H), 3.88 (s, 3H), 3.60-4.00 (m, 7H), 3.04-3.58 (m, 5H), 2.44-  
10 2.92 (m, 5H), 1.28-2.15 (m, 5H), 1.08 (m, 2H).  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  16.3.

#### Example 18

Diethyl phosphonate 20: A solution of phenol 17 (66 mg, 0.1 mmol) and diethyl trifluoromethansulfonyloxymethanphosphonate XY (46 mg, 0.15 mmol) in  $\text{CH}_3\text{CN}$  (1.5 mL) at  
15 room temperature was treated  $\text{Cs}_2\text{CO}_3$  (66 mg, 0.2 mmol). The mixture was stirred for 3 h and partitioned in  $\text{CH}_2\text{Cl}_2$  and saturated  $\text{NaHCO}_3$ . The organic layer was washed with 0.1N HCl, saturated NaCl, dried ( $\text{MgSO}_4$ ), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (10% MeOH/ $\text{CH}_2\text{Cl}_2$ ) affording the unreacted 17 (17 mg, 26%) and diethyl phosphonate 20 (24.5 mg, 41%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$   
20 8.00 (s, 1H), 7.70 (d, 2H), 7.16 (d, 2H), 7.00 (d, 2H), 6.88 (d, 2H), 5.66 (d, 1H), 4.98-5.10 (m, 2H), 4.39 (m, 1H), 4.24 (m, 5H), 3.89 (s, 3H), 3.602-3.98 (m, 7H), 2.55-3.16 (m, 8H), 1.50-2.00 (m, 7H), 1.36 (t, 6H), 1.08 (m, 2H).  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.2

#### Example 19

25 N-methyl piperidine diethyl phosphonate 21: A solution of compound 20 (22.2 mg, 0.0278 mmol) in THF (1.5 mL) at  $0^\circ\text{C}$  was treated with a solution of borane in THF (1M, 0.083 mL). The mixture was stirred for 2 h at room temperature and the starting material was consumed completely as monitored by TLC. The reaction mixture was cooled in an ice/water bath and excess methanol (1 mL) was added to quench the reaction. The solution was concentrated in  
30 vacuo and the crude product was chromatographed on silica gel with MeOH/EtOAc to afford compound 21 (7 mg, 32%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.70 (d, 2H), 7.16 (d, 2H), 7.00 (d, 2H), 6.88

(d, 2H), 5.66 (d, 1H), 4.98-5.10 (m, 2H), 4.24 (m, 4H), 3.89 (s, 3H), 3.602-3.98 (m, 7H),  
2.62-3.15 (m, 9H), 2.26 (s, 3H), 1.52-2.15 (m, 10H), 1.36 (t, 6H).  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.3

## Example Section G

### Example 1

Compound 1: To a solution of 4-nitrobenzyl bromide (21.6 g, 100 mmol) in toluene (100 mL) was added triethyl phosphite (17.15 mL, 100 mmol). The mixture was heated at 120°C for 14 hrs. The evaporation under reduced pressure gave a brown oil, which was purified by flash column chromatography (hexane/EtOAc= 2/1 to 100 % EtOAc) to afford compound 1.

### Example 2

Compound 2: To a solution of compound 1 (1.0 g) in ethanol (60 mL) was added 10% Pd-C (300 mg). The mixture was hydrogenated for 14 hrs. Celite was added and the mixture was stirred for 5 mins. The mixture was filtered through a pad of celite, and washed with ethanol. Concentration gave compound 2.

### Example 3

Compound 3: To a solution of compound 3 (292 mg, 1.2 mmol) and aldehyde (111 mg, 0.2 mmol) in methanol (3 mL) was added acetic acid (48  $\mu$ L, 0.8 mmol). The mixture was stirred for 5 mins, and sodium cyanoborohydride (25 mg, 0.4 mmol) was added. The mixture was stirred for 14 hrs, and methanol was removed under reduced pressure. Water was added, and was extracted with EtOAc. The organic phase was washed 0.5 N NaOH solution (1x), water (2x), and brine (1x), and was dried over MgSO<sub>4</sub>. Purification by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH = 100/3) gave compound 3.

### Example 4

Compound 4: To a solution of compound 3 (79 mg, 0.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added trifluoroacetic acid (1 mL). The mixture was stirred for 2 hrs, and solvents were evaporated under reduced pressure. Coevaporation with EtOAc and CH<sub>2</sub>Cl<sub>2</sub> gave an oil. The oil was dissolved in THF (1mL) and tetrabutylammonium fluoride (0.9 mL, 0.9 mmol) was added. The mixture was stirred for 1 hr, and solvent was removed. Purification by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH = 100/7) gave compound 4.

### Example 5

Compound 5: To a solution of compound 4 (0.1 mmol) in acetonitrile (1 mL) at 0°C was added DMAP (22 mg, 0.18 mmol), followed by bisfurancarboxylate (27 mg, 0.09 mmol). The mixture was stirred for 3 hrs at 0°C, and diluted with EtOAc. The organic phase was washed

with 0.5 N NaOH solution (2x), water (2x), and brine (1x), and dried over  $\text{MgSO}_4$ .

Purification by flash column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH} = 100/3$  to  $100/5$ ) afford compound 5 (50 mg):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.70 (2 H, d,  $J = 8.9$  Hz), 7.11 (2 H, d,  $J = 8.5$  Hz), 6.98 (2 H, d,  $J = 8.9$  Hz), 6.61 (2 H, d,  $J = 8.5$  Hz), 5.71 (1 H, d,  $J = 5.2$  Hz), 5.45 (1 H, m), 5.13 (1 H, m), 4.0 (6 H, m), 3.98-3.70 (4 H, m), 3.86 (3 H, s), 3.38 (2 H, m), 3.22 (1 H, m), 3.02 (5 H, m), 2.8 (1 H, m), 2.0-1.8 (3 H, m), 1.26 (6 H, t,  $J = 7.0$  Hz), 0.95 (3 H, d,  $J = 6.7$  Hz), 0.89 (3 H, d,  $J = 6.7$  Hz).

#### Example 6

- 10 Compound 6: To a solution of compound 5 (30 mg, 0.04 mmol) in MeOH (0.8 mL) was added 37% formaldehyde (30  $\mu\text{L}$ , 0.4 mmol), followed by acetic acid (23  $\mu\text{L}$ , 0.4 mmol). The mixture was stirred for 5 mins, and sodium cyanoborohydride (25 mg, 0.4 mmol) was added. The reaction mixture was stirred for 14 hrs, and diluted with EtOAc. The organic phase was washed 0.5 N NaOH solution (2x), water (2x), and brine, and dried over  $\text{MgSO}_4$ . Purification
- 15 by flash column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH} = 100/3$ ) gave compound 6 (11 mg):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.60 (2 H, d,  $J = 8.9$  Hz), 7.17 (2 H, m), 6.95 (2 H, d,  $J = 8.9$  Hz), 6.77 (2 H, d,  $J = 8.5$  Hz), 5.68 (1 H, d,  $J = 5.2$  Hz), 5.21 (1 H, m), 5.09 (1 H, m), 4.01 (6 H, m), 3.87 (3 H, s), 3.8-3.3 (4 H, m), 3.1-2.6 (7 H, m), 2.90 (3 H, s), 1.8 (3 H, m), 1.25 (6 H, m), 0.91 (6 H, m).

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#### Example 7

- Compound 7: To a solution of compound 1 (24.6 g, 89.8 mmol) in acetonitrile (500 mL) was added TMSBr (36 mL, 269 mmol). The reaction mixture was stirred for 14 hrs, and evaporated under reduced pressure. The mixture was coevaporated with MeOH (2x), toluene
- 25 (2x), EtOAc (2x), and  $\text{CH}_2\text{Cl}_2$  to give a yellow solid (20 g). To the suspension of above yellow solid (15.8 g, 72.5 mmol) in toluene (140 mL) was added DMF (1.9 mL), followed by thionyl chloride (53 mL, 725 mmol). The reaction mixture was heated at  $60^\circ\text{C}$  for 5 hrs, and evaporated under reduced pressure. The mixture was coevaporated with toluene (2x), EtOAc, and  $\text{CH}_2\text{Cl}_2$  (2x) to afford a brown solid. To the solution of the brown solid in
- 30  $\text{CH}_2\text{Cl}_2$  at  $0^\circ\text{C}$  was added benzyl alcohol (29 mL, 290 mmol), followed by slow addition of pyridine (35 mL, 435 mmol). The reaction mixture was allowed to warm to  $25^\circ\text{C}$  and stirred for 14 hrs. Solvents were removed under reduced pressure. The mixture was diluted with EtOAc, and washed with water (3x) and brine (1x), and dried over  $\text{MgSO}_4$ . Concentration

gave a dark oil, which was purified by flash column chromatography (hexanes/EtOAc = 2/1 to 1/1) to afford compound 7.

#### Example 8

- 5 Compound 8: To a solution of compound 7 (15.3 g) in acetic acid (190 mL) was added Zinc dust (20 g). The mixture was stirred for 14 hrs, and celite was added. The suspension was filtered through a pad of celite, and washed with EtOAc. The solution was concentrated under reduced pressure to dryness. The mixture was diluted with EtOAc, and was washed with 2N NaOH (2x), water (2x), and brine (1x), and dried over MgSO<sub>4</sub>. Concentration under  
10 reduced pressure gave compound 8 as an oil (15 g).

#### Example 9

- Compound 9: To a solution of compound 8 (13.5 g, 36.8 mmol) and aldehyde (3.9 g, 7.0 mmol) in methanol (105 mL) was added acetic acid (1.68 mL, 28 mmol). The mixture was  
15 stirred for 5 mins, and sodium cyanoborohydride (882 mg, 14 mmol) was added. The mixture was stirred for 14 hrs, and methanol was removed under reduced pressure. Water was added, and was extracted with EtOAc. The organic phase was washed 0.5 N NaOH solution (1x), water (2x), and brine (1x), and was dried over MgSO<sub>4</sub>. Purification by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH = 100/3) gave compound 9 (6.0 g).

20

#### Example 10

- Compound 10: To a solution of compound 9 (6.2 g, 6.8 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was added trifluoroacetic acid (20 mL). The mixture was stirred for 2 hrs, and solvents were evaporated under reduced pressure. Coevaporation with EtOAc and CH<sub>2</sub>Cl<sub>2</sub> gave an oil. The  
25 oil was dissolved in THF (1mL) and tetrabutylammonium fluoride (0.9 mL, 0.9 mmol) was added. The mixture was stirred for 1 hr, and solvent was removed. Purification by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH = 100/7) gave compound 10.

#### Example 11

- 30 Compound 11: To a solution of compound 10 (5.6 mmol) in acetonitrile (60 mL) at 0°C was added DMAP (1.36g, 11.1 mmol), followed by bisfurancarbonate (1.65 g, 5.6 mmol). The mixture was stirred for 3 hrs at 0°C, and diluted with EtOAc. The organic phase was washed with 0.5 N NaOH solution (2x), water (2x), and brine (1x), and dried over MgSO<sub>4</sub>.

Purification by flash column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH} = 100/3$  to  $100/5$ ) afford compound 11 (3.6 g):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.70 (2 H, d,  $J = 8.9$  Hz), 7.30 (10 H, m), 7.07 (2 H, m), 6.97 (2 H, d,  $J = 8.9$  Hz), 6.58 (2 H, d,  $J = 8.2$  Hz), 5.70 (1 H, d,  $J = 5.2$  Hz), 5.42 (1 H, m), 5.12 (1 H, m), 4.91 (4 H, m), 4.0-3.7 (6 H, m), 3.85 (3 H, s), 3.4 (2 H, m), 3.25 (1 H, m), 3.06 (2 H, d,  $J = 21$  Hz), 3.0 (3 H, m), 2.8 (1 H, m), 1.95 (1 H, m), 1.82 (2 H, m), 0.91 (6 H, m).

#### Example 12

Compound 12: To a solution of compound 11 (3.6 g) in ethanol (175 mL) was added 10% Pd-C (1.5 g). The reaction mixture was hydrogenated for 14 hrs. The mixture was stirred with celite for 5 mins, and filtered through a pad of celite. Concentration under reduced pressure gave compound 12 as a white solid (2.8 g):  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  7.68 (2 H, m), 7.08 (2 H, m), 6.93 (2 H, m), 6.48 (2 H, m), 5.95 (1 H, m), 5.0 (2 H, m), 3.9-3.6 (6 H, m), 3.82 (3 H, s), 3.25 (3 H, m), 3.05 (4 H, m), 2.72 (2 H, d,  $J = 20.1$  Hz), 2.0-1.6 (3 H, m), 0.81 (6 H, m).

#### Example 13

Compound 13: Compound 12 (2.6 g, 3.9 mmol) and L-alanine ethyl ester hydrochloride (3.575 g, 23 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in pyridine (20 mL) and diisopropylethylamine (4.1 mL, 23 mmol) was added. To above mixture was added a solution of Aldrithiol (3.46 g, 15.6 mmol) and triphenylphosphine (4.08 g, 15.6 g) in pyridine (20 mL). The reaction mixture was stirred for 20 hrs, and solvents were evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with 0.5 N NaOH solution (2x), water (2x), and brine, and dried over  $\text{MgSO}_4$ . Concentration under reduced pressure gave a yellow oil, which was purified by flash column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH} = 100/5$  to  $100/10$ ) to afford compound 13 (750 mg):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71 (2 H, d,  $J = 8.8$  Hz), 7.13 (2 H, m), 6.98 (2 H, d,  $J = 8.8$  Hz), 6.61 (2 H, d,  $J = 8.0$  Hz), 5.71 (1 H, d,  $J = 5.2$  Hz), 5.54 (1 H, m), 5.16 (1 H, m), 4.15 (6 H, m), 4.1-3.6 (6 H, m), 3.86 (3 H, s), 3.4-3.2 (3 H, m), 3.1-2.8 (8 H, m), 2.0 (1 H, m), 1.82 (2 H, m), 1.3 (12 H, m), 0.92 (6 H, m).

#### Example 14

Compound 14: To a solution of 4-hydroxypiperidine (19.5 g, 193 mmol) in THF at  $0^\circ\text{C}$  was



added sodium hydroxide solution (160 mL, 8.10 g, 203 mmol), followed by di-tert-butyl dicarbonate (42.1 g, 193 mmol). The mixture was warmed to 25°C, and stirred for 12 hours. THF was removed under reduced pressure, and the aqueous phase was extracted with EtOAc (2x). The combined organic layer was washed with water (2x) and brine, and dried over  
5 MgSO<sub>4</sub>. Concentration gave a compound 14 as a white solid (35 g).

#### Example 15

Compound 15: To a solution of alcohol 14 (5.25 g, 25 mmol) in THF (100 mL) was added sodium hydride (1.2 g, 30 mmol, 60%). The suspension was stirred for 30 mins, and  
10 chloromethyl methyl sulfide (2.3 mL, 27.5 mmol) was added. Starting material alcohol 14 still existed after 12 hrs. Dimethyl sulfoxide (50 mL) and additional chloromethyl methyl sulfide (2.3 mL, 27.5 mmol) were added. The mixture was stirred for additional 3 hrs, and THF was removed under reduced pressure. The reaction was quenched with water, and extracted with ethyl acetate. The organic phase was washed with water and brine, and was  
15 dried over MgSO<sub>4</sub>. Purification by flash column chromatography (hexanes/EtOAc = 8/1) gave compound 15 (1.24 g).

#### Example 16

Compound 16: To a solution of compound 15 (693 mg, 2.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) at -  
20 78°C was added a solution of sulfonyl chloride (214 µL, 2.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL). The reaction mixture was kept at -78°C for 3 hrs, and solvents were removed to give a white solid. The white solid was dissolved in toluene (7 mL), and triethyl phosphite (4.5 mL, 26.6 mmol) was added. The reaction mixture was heated at 120°C for 12 hrs. Solvent and excess reagent was removed under reduced pressure to give compound 16.

25

#### Example 17

Compound 17: To a solution of compound 17 (600 mg) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred for 2 hrs, and was concentrated under reduced pressure to give an oil. The oil was diluted with methylene chloride and base resin  
30 was added. The suspension was filtered and the organic phase was concentrated to give compound 17.

#### Example 18

Compound 18: To a solution of compound 17 (350 mg, 1.4 mmol) and aldehyde (100 mg, 0.2 mmol) in methanol (4 mL) was added acetic acid (156  $\mu$ L, 2.6 mmol). The mixture was stirred for 5 mins, and sodium cyanoborohydride (164 mg, 2.6 mmol) was added. The mixture was stirred for 14 hrs, and methanol was removed under reduced pressure. Water was added, and was extracted with EtOAc. The organic phase was washed 0.5 N NaOH solution (1x), water (2x), and brine (1x), and was dried over  $MgSO_4$ . Purification by flash column chromatography ( $CH_2Cl_2/MeOH = 100/3$ ) gave compound 18 (62 mg).

#### Example 19

Compound 19: To a solution of compound 18 (62 mg, 0.08 mmol) in THF (3 mL) were added acetic acid (9  $\mu$ L, 0.15 mmol) and tetrabutylammonium fluoride (0.45 mL, 1.0 N, 0.45 mmol). The mixture was stirred for 3 hr, and solvent was removed. Purification by flash column chromatography ( $CH_2Cl_2/MeOH = 100/5$ ) gave an oil. To a solution of above oil in  $CH_2Cl_2$  (2 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred for 1 hrs, and was concentrated under reduced pressure. Coevaporation with EtOAc and  $CH_2Cl_2$  gave compound 19.

#### Example 20

Compound 20: To a solution of compound 19 (55 mg 0.08 mmol) in acetonitrile (1 mL) at 0°C was added DMAP (20 mg, 0.16 mmol), followed by bisfurancarboxylate (24 mg, 0.08 mmol). The mixture was stirred for 3 hrs at 0°C, and diluted with EtOAc. The organic phase was washed with 0.5 N NaOH solution (2x), water (2x), and brine (1x), and dried over  $MgSO_4$ . Purification by flash column chromatography ( $CH_2Cl_2/MeOH = 100/3$  to  $100/5$ ) afford compound 20 (46 mg):  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.70 (2 H, d, J = 8.9 Hz), 7.01 (2 H, d, J = 8.9 Hz), 5.73 (1 H, d, J = 5.1 Hz), 5.51 (1 H, m), 5.14 (1 H, m), 4.16 (1 H, m), 4.06 (1 H, m), 3.94 (3 H, m), 3.86 (3 H, s), 3.80 (1 H, m), 3.75 (2 H, d, J = 9.1 Hz), 3.58 (1 H, m), 3.47 (1 H, m), 3.30 (1 H, m), 3.1-2.6 (8 H, m), 2.3 (2 H, m), 2.1-1.8 (5 H, m), 1.40 (2 H, m), 1.36 (6 H, t, J = 7.0 Hz), 0.93 (3 H, d, J = 6.7 Hz), 0.86 (3 h, d, J = 6.7 Hz).

#### Example 21

Compound 21: Compound 21 was made from Boc-4-Nitro-L-Phenylalanine (Fluka) following the procedure for Compound 2 in Scheme Section A, Scheme 1.

Example 22

Compound 22: To a solution of chloroketone 21 (2.76 g, 8 mmol) in THF (50 mL) and water (6 mL) at 0°C (internal temperature) was added solid NaBH<sub>4</sub> (766 mg, 20 mmol) in several portions over a period of 15 min while maintaining the internal temperature below 5°C. The mixture was stirred for 1.5 hrs at 0°C and solvent was removed under reduced pressure. The mixture was quenched with saturated KHSO<sub>3</sub> and extracted with EtOAc. The organic phase was washed with water and brine, and dried over MgSO<sub>4</sub>. Concentration gave a solid, which was recrystallized from EtOAc/hexane (1/1) to afford the chloroalcohol 22 (1.72 g).

Example 23

Compound 23: To a suspension of chloroalcohol 22 (1.8 g, 5.2 mmol) in EtOH (50 mL) was added a solution of KOH in ethanol (8.8 mL, 0.71 N, 6.2 mmol). The mixture was stirred for 2 h at room temperature and ethanol was removed under reduced pressure. The reaction mixture was diluted with EtOAc, and washed with water (2x), saturated NH<sub>4</sub>Cl (2x), water, and brine, and dried over MgSO<sub>4</sub>. Concentration under reduced pressure afforded epoxide 23 (1.57g) as a white crystalline solid.

Example 24

Compound 24: To a solution of epoxide 23 (20 g, 65 mmol) in 2-propanol (250 mL) was added isobutylamine (65 mL) and the solution was refluxed for 90 min. The reaction mixture was concentrated under reduced pressure and was coevaporated with MeOH, CH<sub>3</sub>CN, and CH<sub>2</sub>Cl<sub>2</sub> to give a white solid. To a solution of the white solid in CH<sub>2</sub>Cl<sub>2</sub> (300 mL) at 0°C was added triethylamine (19 mL, 136 mmol), followed by the addition of 4-methoxybenzenesulfonyl chloride (14.1 g, 65 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The reaction mixture was stirred at 0°C for 30 min, and warmed to room temperature and stirred for additional 2 hrs. The reaction solution was concentrated under reduced pressure and was diluted with EtOAc. The organic phase was washed with saturated NaHCO<sub>3</sub>, water and brine, and dried over MgSO<sub>4</sub>. Concentration under reduced pressure gave compound 24 as a white solid (37.5 g).

Example 25

Compound 25: To a solution of compound 24 (37.5 g, 68 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) at 0°C was added a solution of tribromoborane in CH<sub>2</sub>Cl<sub>2</sub> (340 mL, 1.0 N, 340 mmol). The reaction

mixture was kept at 0°C for 1 hr, and warmed to room temperature and stirred for additional 3 hrs. The mixture was cooled to 0°C, and methanol (200 mL) was added slowly. The mixture was stirred for 1 hr and solvents were removed under reduced pressure to give a brown oil. The brown oil was coevaporated with EtOAc and toluene to afford compound 25  
5 as a brown solid, which was dried under vacuum for 48 hrs.

#### Example 26

Compound 26: To a solution of compound 25 in THF (80 mL) was added a saturated sodium bicarbonate solution (25 mL), followed by a solution of Boc<sub>2</sub>O (982 mg, 4.5 mmol) in THF  
10 (20 mL). The reaction mixture was stirred for 5 hrs. THF was removed under reduced pressure, and aqueous phase was extracted with EtOAc. The organic phase was washed with water (2x) and Brine (1x), and dried over MgSO<sub>4</sub>. Purification by flash column chromatography (hexanes/EtOAc = 1/1) gave compound 26 (467 mg).

#### Example 27

Compound 27: To a solution of compound 26 (300 mg, 0.56 mmol) in THF (6 mL) was added Cs<sub>2</sub>CO<sub>3</sub> (546 mg, 1.68 mmol), followed by a solution of triflate (420 mg, 1.39 mmol) in THF (2 mL). The reaction mixture was stirred for 1.5 hrs. The mixture was diluted with EtOAc, and washed with water (3x) and brine (1x), and dried over MgSO<sub>4</sub>. Purification by  
20 flash column chromatography (hexanes/EtOAc = 1/1 to 1/3) gave compound 27 (300 mg).

#### Example 28

Compound 28: To a solution of compound 27 (300 mg, 0.38 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred for 2.5 hrs, and was concentrated  
25 under reduced pressure. The mixture was diluted with EtOAc and was washed with 0.5 N NaOH solution (3x), water (2x), and brine (1x), and dried over MgSO<sub>4</sub>. Concentration gave a white solid. To the solution of above white solid in acetonitrile (3 mL) at 0°C was added DMAP (93 mg, 0.76 mmol), followed by bisfurancarboxylate (112 mg, 0.38 mmol). The mixture was stirred for 3 hrs at 0°C, and diluted with EtOAc. The organic phase was washed  
30 with 0.5 N NaOH solution (2x), water (2x), and brine (1x), and dried over MgSO<sub>4</sub>.

Purification by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH = 100/3 to 100/5) afford compound 28 (230 mg): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.16 (2 H, d, J = 8.5 Hz), 7.73 (2 H, d, J = 9.2 Hz), 7.42 (2 H, d, J = 8.5 Hz), 7.10 (2 H, d, J = 9.2 Hz), 5.65 (1 H, d, J = 4.8 Hz), 5.0 (2 H,

m), 4.34 (2 H, d, J = 10 Hz), 4.25 (4 H, m), 4.0-3.6 (6 H, m), 3.2-2.8 (7 H, m), 1.82 (1 H, m), 1.6 (2 H, m), 1.39 (6 H, t, J = 7.0 Hz), 0.95 (6 H, m).

#### Example 29

- 5 Compound 29: To a solution of compound 28 (50 mg) in ethanol (5 mL) was added 10% Pd-C (20 mg). The mixture was hydrogenated for 5 hrs. Celite was added, and the mixture was stirred for 5 mins. The reaction mixture was filtered through a pad of celite. Concentration under reduced pressure gave compound 29 (50 mg): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.72 (2 H, d, J = 8.8 Hz), 7.07 (2 H, 2 H, d, J = 8.8 Hz), 7.00 (2 H, d, J = 8.5 Hz), 6.61 (2 H, d, J = 8.5 Hz), 5.67 (1  
10 H, d, J = 5.2 Hz), 5.05 (1 H, m), 4.90 (1 H, m), 4.34 (2 H, d, J = 10.3 Hz), 4.26 (2 H, m), 4.0-3.7 (6 H, m), 3.17 (1 H, m), 2.95 (4 H, m), 2.75 (2 H, m), 1.82 (1 H, m), 1.65 (2 H, m), 1.39 (6 H, t, J = 7.0 Hz), 0.93 (3 h, d, J = 6.4 Hz), 0.87 (3 h, d, J = 6.4 Hz).

#### Example 30

- 15 Compound 30: To a solution of compound 29 (50 mg, 0.07 mmol) and formaldehyde (52 μL, 37%, 0.7 mmol) in methanol (1 mL) was added acetic acid (40 μL, 0.7 mmol). The mixture was stirred for 5 mins, and sodium cyanoborohydride (44 mg, 0.7 mmol) was added. The mixture was stirred for 14 hrs, and methanol was removed under reduced pressure. Water was added, and was extracted with EtOAc. The organic phase was washed 0.5 N NaOH  
20 solution (1x), water (2x), and brine (1x), and was dried over MgSO<sub>4</sub>. Purification by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH = 100/3) gave compound 30 (40 mg): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.73 (2 H, d, J = 8.9 Hz), 7.10 (4 H, m), 6.66 (2 H, d, J = 8.2 Hz), 5.66 (1 H, d, J = 5.2 Hz), 5.02 (1 H, m), 4.88 (1 H, m), 4.32 (2 H, d, J = 10.1 Hz), 4.26 (4 H, m), 3.98 (1 H, m), 3.85 (3 H, m), 3.75 (2 H, m), 3.19 (1 H, m), 2.98 (4 H, m), 2.93 (6 H, s), 2.80 (2 H, m),  
25 1.82 (1 H, m), 1.62 (2 H, m), 1.39 (6 H, t, J = 7.0 Hz), 0.90 (6 H, m).

#### Example 31

- Compound 31: To a suspension of compound 25 (2.55 g, 5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) at 0°C was added triethylamine (2.8 mL, 20 mmol), followed by TMSCl (1.26 mL, 10 mmol). The  
30 mixture was stirred at 0°C for 30 mins, and warmed to 25°C and stirred for additional 1 hr. Concentration gave a yellow solid. The yellow solid was dissolved in acetonitrile (30 mL) and cooled to 0°C. To this solution was added DMAP (1.22 g, 10 mmol) and Bisfurancarboxylate (1.48 g, 5 mmol). The reaction mixture was stirred at 0°C for 2 hrs and for

additional 1 hr at 25°C. Acetonitrile was removed under reduced pressure. The mixture was diluted with EtOAc, and washed with 5% citric acid (2x), water (2x), and brine (1x), and dried over MgSO<sub>4</sub>. Concentration gave a yellow solid. The yellow solid was dissolved in THF (40 mL), and acetic acid (1.3 mL, 20 mmol) and tetrabutylammonium fluoride (8mL, 1.0 N, 8mmol) were added. The mixture was stirred for 20 mins, and THF was removed under reduced pressure. Purification by flash column chromatography (hexanes/EtOAc = 1/1) gave compound 31 (1.5 g).

#### Example 32

Compound 32: To a solution of compound 31 (3.04 g, 5.1 mmol) in THF (75 mL) was added Cs<sub>2</sub>CO<sub>3</sub> (3.31 g, 10.2 mmol), followed by a solution of triflate (3.24 g, 7.65 mmol) in THF (2 mL). The reaction mixture was stirred for 1.5 hrs, and THF was removed under reduced pressure. The mixture was diluted with EtOAc, and washed with water (3x) and brine (1x), and dried over MgSO<sub>4</sub>. Purification by flash column chromatography (hexanes/EtOAc = 1/1 to 1/3) gave compound 32 (2.4 g): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.17 (2 H, d, J = 8.5 Hz), 7.70 (2 H, J = 9.2 Hz), 7.43 (2 H, d, J = 8.5 Hz), 7.37 (10 H, m), 6.99 (2 H, d, J = 9.2 Hz), 5.66 (1 H, d, J = 5.2 Hz), 5.15 (4 H, m), 5.05 (2 H, m), 4.26 (2 H, d, J = 10.2 Hz), 3.9-3.8 (4 H, m), 3.75 (2 H, m), 3.2-2.8 (7 H, m), 1.82 (1 H, m), 1.62 (2 H, m), 0.92 (6 H, m).

#### Example 33

Compound 33: To a solution of compound 32 (45 mg) in acetic acid (3 mL) was added zinc (200 mg). The mixture was stirred for 5 hrs. Celite was added, and the mixture was filtered and washed with EtOAc. The solution was concentrated to dryness and diluted with EtOAc. The organic phase was washed with 0.5 N NaOH solution, water, and brine, and dried over MgSO<sub>4</sub>. Purification by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/isopropanol = 100/5) gave compound 33 (25 mg): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.67 (2 H, d, J = 8.8 Hz), 7.36 (10 H, m), 6.98 (4 H, m), 6.60 (2 H, d, J = 8.0 Hz), 5.67 (1 H, d, J = 4.9 Hz), 5.12 (4 H, m), 5.05 (1 H, m), 4.90 (1 H, m), 4.24 (2 H, d, J = 10.4 Hz), 4.0-3.6 (6 H, m), 3.12 (1 H, m), 3.95 (4 H, m), 2.75 (2 H, m), 1.80 (1 H, m), 1.2 (2 H, m), 0.9 (6 H, m).

#### Example 34

Compound 34: To a solution of compound 32 (2.4 g) in ethanol (140 mL) was added 10% Pd-C (1.0 g). The mixture was hydrogenated for 14 hrs. Celite was added, and the mixture

was stirred for 5 mins. The slurry was filtered through a pad of celite, and washed with pyridine. Concentration under reduced pressure gave compound 34:  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  7.67 (2 H, d,  $J = 8.9$  Hz), 7.14 (2 H, d,  $J = 8.9$  Hz), 6.83 (2 H, d,  $J = 8.0$  Hz), 6.41 (2 H, d,  $J = 8.0$  Hz), 5.51 (1 H, d,  $J = 5.2$  Hz), 5.0–4.8 (2 H, m), 4.15 (2 H, d,  $J = 10.0$  Hz), 3.9–3.2 (8 H, m), 3.0 (2 H, m), 2.8 (4 H, m), 2.25 (1 H, m), 1.4 (2 H, m), 0.8 (6 H, m).

#### Example 35

Compound 35: Compound 34 (1.62 g, 2.47 mmol) and L-alanine butyl ester hydrochloride (2.69 g, 14.8 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in pyridine (12 mL) and diisopropylethylamine (2.6 mL, 14.8 mmol) was added. To above mixture was added a solution of Aldrithiol (3.29 g, 14.8 mmol) and triphenylphosphine (3.88 g, 14.8 mmol) in pyridine (12 mL). The reaction mixture was stirred for 20 hrs, and solvents were evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with 0.5 N NaOH solution (2x), water (2x), and brine, and dried over  $\text{MgSO}_4$ . Concentration under reduced pressure gave a yellow oil, which was purified by flash column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH} = 100/5$  to  $100/15$ ) to afford compound 35 (1.17 g):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.70 (2 H, d,  $J = 8.6$  Hz), 7.05 (2 H, d,  $J = 8.6$  Hz), 6.99 (2 H, d,  $J = 8.0$  Hz), 6.61 (2 H, d,  $J = 8.0$  Hz), 5.67 (1 H, d,  $J = 5.2$  Hz), 5.05 (1 H, m), 4.96 (1 H, m), 4.28 (2 H, m), 4.10 (6 H, m), 4.0–3.6 (6 H, m), 3.12 (2 H, m), 2.92 (3 H, m), 2.72 (2 H, m), 1.82 (1 H, m), 1.75–1.65 (2 H, m), 1.60 (4 H, m), 1.43 (6 H, m), 1.35 (4 H, m), 0.91 (12 H, m).

#### Example 36

Compound 37: Compound 36 (100 mg, 0.15 mmol) and L-alanine butyl ester hydrochloride (109 mg, 0.60 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in pyridine (1 mL) and diisopropylethylamine (105  $\mu\text{L}$ , 0.6 mmol) was added. To above mixture was added a solution of Aldrithiol (100 mg, 0.45 mmol) and triphenylphosphine (118 mg, 0.45 mmol) in pyridine (1 mL). The reaction mixture was stirred for 20 hrs, and solvents were evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with water (2x), and brine, and dried over  $\text{MgSO}_4$ . Concentration under reduced pressure gave an oil, which was purified by flash column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH} = 100/5$  to  $100/15$ ) to afford compound 37 (21 mg):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71 (2 H, d,  $J = 8.8$  Hz), 7.15 (2 H, d,  $J = 8.2$  Hz), 7.01 (2 H, d,  $J = 8.8$  Hz), 6.87 (2 H, d,  $J = 8.2$  Hz), 5.66 (1 H, d,  $J = 5.2$  Hz), 5.03 (1 H, m), 4.95 (1 H, m), 4.2–4.0 (8 H, m), 3.98 (1 H, m), 3.89 (3 H, s),

3.88-3.65 (5 H, m), 3.15 (1 H, m), 2.98 (4 H, m), 2.82 (2 H, m), 1.83 (1 H, m), 1.63 (4 H, m), 1.42 (6 H, m), 1.35 (4 H, m), 0.95 (12 H, m).

#### Example 37

- 5 Compound 38: Compound 36 (100 mg, 0.15 mmol) and L-leucine ethyl ester hydrochloride (117 mg, 0.60 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in pyridine (1 mL) and diisopropylethylamine (105  $\mu$ L, 0.6 mmol) was added. To above mixture was added a solution of Aldrithiol (100 mg, 0.45 mmol) and triphenylphosphine (118 mg, 0.45 mmol) in pyridine (1 mL). The reaction mixture was stirred for 20 hrs, and solvents  
10 were evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with water (2x), and brine, and dried over  $MgSO_4$ . Concentration under reduced pressure gave an oil, which was purified by flash column chromatography ( $CH_2Cl_2/MeOH = 100/5$  to  $100/15$ ) to afford compound 38 (12 mg):  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.72 (2 H, d,  $J = 8.5$  Hz), 7.14 (2 H, d,  $J = 8.0$  Hz), 7.00 (2 H, d,  $J = 8.5$  Hz), 6.86 (2 H, d,  $J = 8.0$  Hz), 5.66 (1 H, d,  $J = 5.2$  Hz), 5.05 (1 H, m), 4.95 (1 H, m), 4.2-4.0 (8 H, m), 4.0-3.68 (6 H, m), 3.88 (3 H, s),  
15 3.2-2.9 (5 H, m), 2.80 (2 H, m), 1.80 (1 H, m), 1.65 (4 H, m), 1.65-1.50 (4 H, m), 1.24 (6 H, m), 0.94 (18 H, m).

#### Example 38

- 20 Compound 39: Compound 36 (100 mg, 0.15 mmol) and L-leucine butyl ester hydrochloride (117 mg, 0.60 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in pyridine (1 mL) and diisopropylethylamine (105  $\mu$ L, 0.6 mmol) was added. To above mixture was added a solution of Aldrithiol (100 mg, 0.45 mmol) and triphenylphosphine (118 mg, 0.45 mmol) in pyridine (1 mL). The reaction mixture was stirred for 20 hrs, and solvents  
25 were evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with water (2x), and brine, and dried over  $MgSO_4$ . Concentration under reduced pressure gave an oil, which was purified by flash column chromatography ( $CH_2Cl_2/MeOH = 100/5$  to  $100/15$ ) to afford compound 39 (32 mg):  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.72 (2 H, d,  $J = 8.8$  Hz), 7.15 (2 H, d,  $J = 8.0$  Hz), 7.0 (2 H, d,  $J = 8.8$  Hz), 6.89 (2 H, d,  $J = 8.0$  Hz), 5.66 (1 H, d,  $J = 4.3$  Hz), 5.07 (1 H, m), 4.94 (1 H, m), 4.2-4.0 (8 H, m), 3.89 (3 H, s), 4.0-3.6 (6 H, m),  
30 3.2-2.9 (5 H, m), 2.8 (2 H, m), 1.81 (1 H, m), 1.78-1.44 (10 H, m), 1.35 (4 H, m), 0.95 (24 H, m).



Example 39

Compound 41: Compound 40 (82 mg, 0.1 mmol) and L-alanine isopropyl ester hydrochloride (92 mg, 0.53 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in pyridine (1 mL) and diisopropylethylamine (136  $\mu$ L, 0.78 mmol) was added. To  
5 above mixture was added a solution of Aldrithiol (72 mg, 0.33 mmol) and triphenylphosphine (87 mg, 0.33 mmol) in pyridine (1 mL). The reaction mixture was stirred at 75°C for 20 hrs, and solvents were evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with water (2x), and brine, and dried over MgSO<sub>4</sub>. Concentration under reduced pressure gave an oil, which was purified by flash column chromatography  
10 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH = 100/1 to 100/3) to afford compound 41 (19 mg): <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.71 (2 H, d, J = 8.9 Hz), 7.2-7.35 (5 H, m), 7.15 (2 H, m), 7.01 (2 H, d, J = 8.9 Hz), 6.87 (2 H, m), 5.65 (1 H, d, J = 5.4 Hz), 5.05-4.93 (2 H, m), 4.3 (2 H, m), 4.19 (1 H, m), 3.98 (1 H, m), 3.88 (3 H, s), 3.80 (2 H, m), 3.70 (3 H, m), 3.18 (1 H, m), 2.95 (4 H, m), 2.78 (2 H, m), 1.82 (1 H, m), 1.62 (2 H, m), 1.35 (3 H, m), 1.25-1.17 (6 H, m), 0.93 (3 H, d, J = 6.4 Hz), 0.88 (3 H, d, J  
15 = 6.4 Hz).

Example 40

Compound 42: Compound 40 (100 mg, 0.13 mmol) and L-glycine butyl ester hydrochloride (88 mg, 0.53 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in  
20 pyridine (1 mL) and diisopropylethylamine (136  $\mu$ L, 0.78 mmol) was added. To above mixture was added a solution of Aldrithiol (72 mg, 0.33 mmol) and triphenylphosphine (87 mg, 0.33 mmol) in pyridine (1 mL). The reaction mixture was stirred at 75°C for 20 hrs, and solvents were evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with water (2x), and brine, and dried over MgSO<sub>4</sub>. Concentration  
25 under reduced pressure gave an oil, which was purified by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH = 100/1 to 100/3) to afford compound 42 (18 mg): <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.71 (2 H, d, J = 9.2 Hz), 7.35-7.24 (5 H, m), 7.14 (2 H, m), 7.00 (2 H, d, J = 8.8 Hz), 6.87 (2 H, m), 5.65 (1 H, d, J = 5.2 Hz), 5.04 (1 H, m), 4.92 (1 H, m), 4.36 (2 H, m), 4.08 (2 H, m), 3.95 (3 H, m), 3.88 (3 H, s), 3.80 (2 H, m), 3.76 (3 H, m), 3.54 (1 H, m), 3.15 (1 H, m), 2.97 (4 H,  
30 m), 2.80 (2 H, m), 1.82 (1 H, m), 1.62 (4 H, m), 1.35 (2 H, m), 0.9 (9 H, m).

## Example Section H

### Example 1

Sulfonamide 1: To a suspension of epoxide (20 g, 54.13 mmol) in 2-propanol (250 mL) was  
5 added isobutylamine (54 mL, 541 mmol) and the solution was refluxed for 30 min. The  
solution was evaporated under reduced pressure and the crude solid was dissolved in CH<sub>2</sub>Cl<sub>2</sub>  
(250 mL) and cooled to 0°C. Triethylamine (15.1 mL, 108.26 mmol) was added followed by  
the addition of 4-nitrobenzenesulfonyl chloride (12 g, 54.13 mmol) and the solution was  
10 stirred for 40 min at 0°C, warmed to room temperature for 2 h, and evaporated under reduced  
pressure. The residue was partitioned between EtOAc and saturated NaHCO<sub>3</sub>. The organic  
phase was washed with saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under  
reduced pressure. The crude product was recrystallized from EtOAc/hexane to give the  
sulfonamide (30.59 g, 90%) as an off-white solid.

### Example 2

Phenol 2: A solution of sulfonamide 1 (15.58 g, 24.82 mmol) in EtOH (450 mL) and CH<sub>2</sub>Cl<sub>2</sub>  
(60 mL) was treated with 10% Pd/C (6 g). The suspension was stirred under H<sub>2</sub> atmosphere  
(balloon) at room temperature for 24 h. The reaction mixture was filtered through a plug of  
celite and concentrated under reduced pressure. The crude product was purified by column  
20 chromatography on silica gel (6% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give the phenol (11.34 g, 90%) as a  
white solid.

### Example 3

Dibenzylphosphonate 3: To a solution of phenol 2 (18.25 g, 35.95 mmol) in CH<sub>3</sub>CN (200  
25 mL) was added Cs<sub>2</sub>CO<sub>3</sub> (23.43 g, 71.90 mmol) and triflate (19.83 g, 46.74 mmol). The  
reaction mixture was stirred at room temperature for 1 h and the solvent was evaporated  
under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl.  
The organic phase was dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure.  
The crude product was purified by column chromatography on silica gel (2/1-EtOAc/hexane)  
30 to give the dibenzylphosphonate (16.87 g, 60%) as a white solid.

### Example 4

Amine 4: A solution of dibenzylphosphonate (16.87 g, 21.56 mmol) in  $\text{CH}_2\text{Cl}_2$  (60 mL) at  $0^\circ\text{C}$  was treated with trifluoroacetic acid (30 mL). The solution was stirred for 30 min at  $0^\circ\text{C}$  and then warmed to room temperature for an additional 30 min. Volatiles were evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH.

- 5 The organic phase was washed with 0.5 N NaOH (2x), water (2x), saturated NaCl, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure to give the amine (12.94 g, 88%) as a white solid.

#### Example 5

- 10 Carbonate 5: To a solution of (S)-(+)-3-hydroxytetrahydrofuran (5.00 g, 56.75 mmol) in  $\text{CH}_2\text{Cl}_2$  (80 mL) was added triethylamine (11.86 mL, 85.12 mmol) and bis(4-nitrophenyl)carbonate (25.90 g, 85.12 mmol). The reaction mixture was stirred at room temperature for 24 h and partitioned between  $\text{CH}_2\text{Cl}_2$  and saturated  $\text{NaHCO}_3$ . The  $\text{CH}_2\text{Cl}_2$  layer was dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude product was purified by
- 15 column chromatography on silica gel (2/1-EtOAc/hexane) to give the carbonate (8.62 g, 60%) as a pale yellow oil which solidified upon refrigerating.

#### Example 6

Carbamate 6: Two methods have been used.

- 20 Method 1: To a solution of 4 (6.8 g, 9.97 mmol) and 5 (2.65 g, 10.47 mmol) in  $\text{CH}_3\text{CN}$  (70 mL) at  $0^\circ\text{C}$  was added 4-(dimethylamino)pyridine (2.44 g, 19.95 mmol). The reaction mixture was stirred at  $0^\circ\text{C}$  for 3 h and concentrated. The residue was dissolved in EtOAc and washed with 0.5 N NaOH, saturated  $\text{NaHCO}_3$ ,  $\text{H}_2\text{O}$ , dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the carbamate (3.97 g, 50%) as a pale yellow solid.
- 25

- Method 2: To a solution of 4 (6.0 g, 8.80 mmol) and 5 (2.34 g, 9.24 mmol) in  $\text{CH}_3\text{CN}$  (60 mL) at  $0^\circ\text{C}$  was added 4-(dimethylamino)pyridine (0.22 g, 1.76 mmol) and N, N-diisopropylethylamine (3.07 mL, 17.60 mmol). The reaction mixture was stirred at  $0^\circ\text{C}$  for 1
- 30 h and warmed to room temperature overnight. The solvent was evaporated under reduced pressure. The crude product was dissolved in EtOAc and washed with 0.5 N NaOH, saturated  $\text{NaHCO}_3$ ,  $\text{H}_2\text{O}$ , dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude product

was purified by column chromatography on silica gel (3% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the carbamate (3.85 g, 55%) as a pale yellow solid.

#### Example 7

- 5    **Phosphonic Acid 7:** To a solution of 6 (7.52 g, 9.45 mmol) in MeOH (350 mL) was added 10% Pd/C (3 g). The suspension was stirred under H<sub>2</sub> atmosphere (balloon) at room temperature for 48 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (5.24 g, 90%) as a white solid.

10

#### Example 8

- Cbz Amide 8:** To a solution of 7 (5.23 g, 8.50 mmol) in CH<sub>3</sub>CN (50 mL) was added N, O-bis(trimethylsilyl)acetamide (16.54 mL, 68 mmol) and then heated to 70°C for 3 h. The reaction mixture was cooled to room temperature and concentrated. The residue was co-  
15    evaporated with toluene and dried under vacuum to afford the silylated intermediate which was used directly without any further purification. To a solution of the silylated intermediate in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) at 0°C was added pyridine (1.72 mL, 21.25 mmol) and benzyl  
      chloroformate (1.33 mL, 9.35 mmol). The reaction mixture was stirred at 0°C for 1 h and warmed to room temperature overnight. A solution of MeOH (50 mL) and 1% aqueous HCl  
20    (150 mL) was added at 0°C and stirred for 30 min. CH<sub>2</sub>Cl<sub>2</sub> was added and two layers were separated. The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated, co-evaporated with toluene, and dried under vacuum to give the Cbz amide (4.46 g, 70%) as an off-white solid.

#### 25    Example 9

- Diphenylphosphonate 9:** A solution of 8 (4.454 g, 5.94 mmol) and phenol (5.591 g, 59.4 mmol) in pyridine (40 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (4.903 g, 23.76 mmol) was added. The reaction mixture was stirred at 70°C for 4 h and cooled to room temperature. EtOAc was added and the side product 1,3-dicyclohexyl urea was filtered off.  
30    The filtrate was concentrated and dissolved in CH<sub>3</sub>CN (20 mL) at 0°C. The mixture was treated with DOWEX 50W x 8-400 ion-exchange resin and stirred for 30 min at 0°C. The resin was filtered off and the filtrate was concentrated. The crude product was purified by

column chromatography on silica gel (4% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the diphenylphosphonate (2.947 g, 55%) as a white solid.

#### Example 10

5 Monophosphonic Acid 10: To a solution of 9 (2.945 g, 3.27 mmol) in  $\text{CH}_3\text{CN}$  (25 mL) at  $0^\circ\text{C}$  was added 1N NaOH (8.2 mL, 8.2 mmol). The reaction mixture was stirred at  $0^\circ\text{C}$  for 1 h. DOWEX 50W x 8-400 ion-exchange resin was added and the reaction mixture was stirred for 30 min at  $0^\circ\text{C}$ . The resin was filtered off and the filtrate was concentrated and co-  
10 evaporated with toluene. The crude product was triturated with EtOAc/hexane (1/2) to give the monophosphonic acid (2.427 g, 90%) as a white solid.

#### Example 11

Cbz Protected Monophosphoamidate 11: A solution of 10 (2.421 g, 2.93 mmol) and L-alanine isopropyl ester hydrochloride (1.969 g, 11.73 mmol) in pyridine (20 mL) was heated  
15 to  $70^\circ\text{C}$  and 1,3-dicyclohexylcarbodiimide (3.629 g, 17.58 mmol) was added. The reaction mixture was stirred at  $70^\circ\text{C}$  for 2 h and cooled to room temperature. The solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with 0.2 N HCl,  $\text{H}_2\text{O}$ , saturated  $\text{NaHCO}_3$ , dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude product was purified by column  
20 chromatography on silica gel (4% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the monoamidate (1.569 g, 57%) as a white solid.

#### Example 12

Monophosphoamidate 12: To a solution of 11 (1.569 g, 1.67 mmol) in EtOAc (80 mL) was  
25 added 10% Pd/C (0.47 g). The suspension was stirred under  $\text{H}_2$  atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and the crude product was purified by column chromatography on silica gel ( $\text{CH}_2\text{Cl}_2$  to 1-8% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the monophosphoamidate 12a (1.12 g, 83%, GS 108577, 1:1 diastereomeric mixture A/B) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.45  
30 (dd, 2H), 7.41-7.17 (m, 7H), 6.88 (dd, 2H), 6.67 (d,  $J = 8.4$  Hz, 2H), 5.16 (broad s, 1H), 4.95 (m, 1H), 4.37-4.22 (m, 5H), 3.82-3.67 (m, 7H), 2.99-2.70 (m, 6H), 2.11-1.69 (m, 3H), 1.38 (m, 3H), 1.19 (m, 6H), 0.92 (d,  $J = 6.3$  Hz, 3H), 0.86 (d,  $J = 6.3$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.5, 19.6. 12b (29 mg, 2%, GS108578, diastereomer A) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )

$\delta$  7.43 (d,  $J = 7.8$  Hz, 2H), 7.35-7.17 (m, 7H), 6.89 (d,  $J = 8.4$  Hz, 2H), 6.67 (d,  $J = 8.4$  Hz, 2H), 5.16 (broad s, 1H), 4.96 (m, 1H), 4.38-4.32 (m, 4H), 4.20 (m, 1H), 3.82-3.69 (m, 7H), 2.99-2.61 (m, 6H), 2.10 (m, 1H), 1.98 (m, 1H), 1.80 (m, 1H), 1.38 (d,  $J = 7.2$  Hz, 3H), 1.20 (d,  $J = 6.3$  Hz, 6H), 0.92 (d,  $J = 6.3$  Hz, 3H), 0.86 (d,  $J = 6.3$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$

5 20.5. 12c (22 mg, 1.6%, GS 108579, diastereomer B) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.45 (d,  $J = 8.1$  Hz, 2H), 7.36-7.20 (m, 7H), 6.87 (d,  $J = 8.7$  Hz, 2H), 6.67 (d,  $J = 8.4$  Hz, 2H), 5.15 (broad s, 1H), 4.95 (m, 1H), 4.34-4.22 (m, 5H), 3.83-3.67 (m, 7H), 2.99-2.64 (m, 6H), 2.11-1.68 (m, 3H), 1.33 (d,  $J = 6.9$  Hz, 3H), 1.20 (d,  $J = 6.0$  Hz, 6H), 0.92 (d,  $J = 6.3$  Hz, 3H), 0.86 (d,  $J = 6.3$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.6.

10

#### Example 13

Sulfonamide 13: To a suspension of epoxide (1.67 g, 4.52 mmol) in 2-propanol (25 mL) was added isobutylamine (4.5 mL, 45.2 mmol) and the solution was refluxed for 30 min. The solution was evaporated under reduced pressure and the crude solid was dissolved in  $\text{CH}_2\text{Cl}_2$  (20 mL) and cooled to  $0^\circ\text{C}$ . Triethylamine (1.26 mL, 9.04 mmol) was added followed by the treatment of 3-nitrobenzenesulfonyl chloride (1.00 g, 4.52 mmol). The solution was stirred for 40 min at  $0^\circ\text{C}$ , warmed to room temperature for 2 h, and evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated  $\text{NaHCO}_3$ . The organic phase was washed with saturated NaCl, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (1/1-EtOAc/hexane) to give the sulfonamide (1.99 g, 70%) as a white solid.

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#### Example 14

Phenol 14: Sulfonamide 13 (1.50 g, 2.39 mmol) was suspended in HOAc (40 mL) and concentrated HCl (20 mL) and heated to reflux for 3 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude product was partitioned between 10% MeOH/ $\text{CH}_2\text{Cl}_2$  and saturated  $\text{NaHCO}_3$ . The organic layers were washed with  $\text{NaHCO}_3$ ,  $\text{H}_2\text{O}$ , dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to give a yellow solid. The crude product was dissolved in  $\text{CHCl}_3$  (20 mL) and treated with triethylamine (0.9 mL, 6.45 mmol) followed by the addition of  $\text{Boc}_2\text{O}$  (0.61 g, 2.79 mmol). The reaction mixture was stirred at room temperature for 6 h. The product was partitioned between  $\text{CHCl}_3$  and  $\text{H}_2\text{O}$ . The  $\text{CHCl}_3$  layer was washed with  $\text{NaHCO}_3$ ,  $\text{H}_2\text{O}$ , dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude product was purified by column chromatography on silica gel (1-5%

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MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give the phenol (0.52 g, 45%) as a pale yellow solid.

#### Example 15

Dibenzylphosphonate 15: To a solution of phenol 14 (0.51 g, 0.95 mmol) in CH<sub>3</sub>CN (8 mL) was added Cs<sub>2</sub>CO<sub>3</sub> (0.77 g, 2.37 mmol) and triflate (0.8 g, 1.90 mmol). The reaction mixture was stirred at room temperature for 1.5 h and the solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give the dibenzylphosphonate (0.62 g, 80%) as a white solid.

#### Example 16

Amine 16: A solution of dibenzylphosphonate 15 (0.61 g, 0.75 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (8 mL) at 0°C was treated with trifluoroacetic acid (2 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. Volatiles were evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5 N NaOH (2x), water (2x), saturated NaCl, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and evaporated under reduced pressure to give the amine (0.48 g, 90%) which was used directly without any further purification.

#### Example 17

Carbamate 17: To a solution of amine 16 (0.48 g, 0.67 mmol) in CH<sub>3</sub>CN (8 mL) at 0°C was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-b]furan-2-yl 4-nitrophenyl carbonate (0.2 g, 0.67 mmol, prepared according to Ghosh et al. J. Med. Chem. 1996, 39, 3278.) and 4-(dimethylamino)pyridine (0.17 g, 1.34 mmol). After stirring for 2 h at 0°C, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5N NaOH (2 x), 5% citric acid (2 x), saturated NaHCO<sub>3</sub>, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the carbamate (0.234 g, 40%) as a white solid.

#### Example 18

Analine 18: To a solution of carbamate 17 (78 mg, 0.09 mmol) in 2 mL HOAc was added zinc powder. The reaction mixture was stirred at room temperature for 1.5 h and filtered through a small plug of celite. The filtrate was concentrated and co-evaporated with toluene. The crude product was purified by column chromatography on silica gel (5% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the analine (50 mg, 66%) as a white solid.

#### Example 19

Phosphonic Acid 19: To a solution of analine (28 mg, 0.033mmol) in MeOH (1 mL) and HOAc (0.5 mL) was added 10% Pd/C (14 mg). The suspension was stirred under H<sub>2</sub> atmosphere (balloon) at room temperature for 6 h. The reaction mixture was filtered through a small plug of celite. The filtrate was concentrated, co-evaporated with toluene, and dried under vacuum to give the phosphonic acid (15 mg, 68%, GS 17424) as a white solid: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 7.16-6.82 (m, 8H), 5.50 (d, 1H), 4.84 (m, 1H), 3.86-3.37 (m, 9H), 2.95-2.40 (m, 6H), 1.98 (m, 1H), 1.42-1.23 (m, 2H), 0.84 (d, J = 6.3 Hz, 3H), 0.79 (d, J = 6.3 Hz, 3H). MS (ESI) 657 (M-H).

#### Example 20

Phenol 21: A suspension of aminohydrobromide salt 20 (22.75 g, 44 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (200 mL) at 0°C was treated with triethylamine (24.6 mL, 176 mmol) followed by slow addition of chlorotrimethylsilane (11.1 mL, 88 mmol). The reaction mixture was stirred at 0°C for 30 min and warmed to room temperature for 1 h. The solvent was removed under reduced pressure to give a yellow solid. The crude product was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (300 mL) and treated with triethylamine (18.4 mL, 132 mmol) and Boc<sub>2</sub>O (12 g, 55 mmol). The reaction mixture was stirred at room temperature overnight. The product was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O. The CH<sub>2</sub>Cl<sub>2</sub> layer was washed with NaHCO<sub>3</sub>, H<sub>2</sub>O, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was dissolved in THF (200 mL) and treated with 1.0 M TBAF (102 mL, 102 mmol) and HOAc (13 mL). The reaction mixture was stirred at room temperature for 1 h and concentrated under reduced pressure. The residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (1-3% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the phenol (13.75 g, 58%) as a white solid.

#### Example 21



Dibenzylphosphonate 22: To a solution of phenol 21 (13.70 g, 25.48 mmol) in THF (200 mL) was added  $\text{Cs}_2\text{CO}_3$  (16.61 g, 56.96 mmol) and triflate (16.22 g, 38.22 mmol). The reaction mixture was stirred at room temperature for 1 h and the solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl.

- 5 The organic phase was dried with  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% MeOH/ $\text{CH}_2\text{Cl}_2$ ) to give the dibenzylphosphonate (17.59 g, 85%) as a white solid.

#### Example 22

- 10 Amine 23: A solution of dibenzylphosphonate 22 (17.58 g, 21.65 mmol) in  $\text{CH}_2\text{Cl}_2$  (60 mL) at  $0^\circ\text{C}$  was treated with trifluoroacetic acid (30 mL). The solution was stirred for 30 min at  $0^\circ\text{C}$  and then warmed to room temperature for an additional 1.5 h. Volatiles were evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5 N NaOH (2x), water (2x), saturated NaCl, dried with
- 15  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure to give the amine (14.64 g, 95%) which was used directly without any further purification.

#### Example 23

- Carbamate 24: To a solution of amine 23 (14.64 g, 20.57 mmol) in  $\text{CH}_3\text{CN}$  (200 mL) at  $0^\circ\text{C}$  was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-b]furan-2-yl 4-nitrophenyl carbonate (6.07 g, 20.57 mmol, prepared according to Ghosh et al., J. Med. Chem. 1996, 39, 3278.) and 4-(dimethylamino)pyridine (5.03 g, 41.14 mmol). After stirring for 2 h at  $0^\circ\text{C}$ , the reaction solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5 N NaOH (2 x), 5% citric acid (2 x), saturated  $\text{NaHCO}_3$ , dried with  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced
- 25 pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the carbamate (10 g, 56%) as a white solid.

#### Example 24

- 30 Phosphonic Acid 25: To a solution of carbamate 24 (8 g, 9.22 mmol) in EtOH (500 mL) was added 10% Pd/C (4 g). The suspension was stirred under  $\text{H}_2$  atmosphere (balloon) at room temperature for 30 h. The reaction mixture was filtered through a plug of celite. The celite paste was suspended in pyridine and stirred for 30 min and filtered. This process was

repeated twice. The combined solution was concentrated under reduced pressure to give the phosphonic acid (5.46 g, 90%) as an off-white solid.

#### Example 25

5    Cbz Amide 26: To a solution of 25 (5.26 g, 7.99 mmol) in CH<sub>3</sub>CN (50 mL) was added N, O-bis(trimethylsilyl)acetamide (15.6 mL, 63.92 mmol) and then heated to 70°C for 3 h. The reaction mixture was cooled to room temperature and concentrated. The residue was co-evaporated with toluene and dried under vacuum to afford the silylated intermediate which was used directly without any further purification. To a solution of the silylated intermediate  
10    in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) at 0°C was added pyridine (1.49 mL, 18.38 mmol) and benzyl chloroformate (1.25 mL, 8.79 mmol). The reaction mixture was stirred at 0°C for 1 h and warmed to room temperature overnight. A solution of MeOH (50 mL) and 1% aqueous HCl (150 mL) was added at 0°C and stirred for 30 min. CH<sub>2</sub>Cl<sub>2</sub> was added and two layers were separated. The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated, co-evaporated  
15    with toluene, and dried under vacuum to give the Cbz amide (4.43 g, 70%) as an off-white solid.

#### Example 26

Diphenylphosphonate 27: A solution of 26 (4.43 g, 5.59 mmol) and phenol (4.21 g, 44.72  
20    mmol) in pyridine (40 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (4.62 g, 22.36 mmol) was added. The reaction mixture was stirred at 70°C for 36 h and cooled to room temperature. EtOAc was added and the side product 1,3-dicyclohexyl urea was filtered off. The filtrate was concentrated and dissolved in CH<sub>3</sub>CN (20 mL) at 0°C. The mixture was treated with DOWEX 50W x 8-400 ion-exchange resin and stirred for 30 min at 0°C. The  
25    resin was filtered off and the filtrate was concentrated. The crude product was purified by column chromatography on silica gel (2/1-EtOAc/hexane to EtOAc) to give the diphenylphosphonate (2.11 g, 40%) as a pale yellow solid.

#### Example 27

30    Monophosphonic Acid 28: To a solution of 27 (2.11 g, 2.24 mmol) in CH<sub>3</sub>CN (15 mL) at 0°C was added 1N NaOH (5.59 mL, 5.59 mmol). The reaction mixture was stirred at 0°C for 1 h. DOWEX 50W x 8-400 ion-exchange resin was added and the reaction mixture was stirred for 30 min at 0°C. The resin was filtered off and the filtrate was concentrated and co-

evaporated with toluene. The crude product was triturated with EtOAc/hexane (1/2) to give the monophosphonic acid (1.75 g, 90%) as a white solid.

#### Example 28

5    Cbz Protected Monophosphoamidate 29: A solution of 28 (1.54 g, 1.77 mmol) and L-alanine isopropyl ester hydrochloride (2.38 g, 14.16 mmol) in pyridine (15 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (2.20 g, 10.62 mmol) was added. The reaction mixture was stirred at 70°C overnight and cooled to room temperature. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc and 0.2 N HCl. The  
10   EtOAc layer was washed with 0.2 N HCl, H<sub>2</sub>O, saturated NaHCO<sub>3</sub>, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give the monophosphoamidate (0.70g, 40%) as an off-white solid.

#### 15    Example 29

Monophosphoamidate 30a-b: To a solution of 29 (0.70 g, 0.71 mmol) in EtOH (10 mL) was added 10% Pd/C (0.3 g). The suspension was stirred under H<sub>2</sub> atmosphere (balloon) at room temperature for 6 h. The reaction mixture was filtered through a small plug of celite. The filtrate was concentrated and the crude products were purified by column chromatography on  
20   silica gel (7-10% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give the monoamidates 30a (0.106 g, 18%, **GS 77369**, 1/1 diastereomeric mixture) as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.71 (d, J = 8.7 Hz, 2H), 7.73-7.16 (m, 5H), 7.10-6.98 (m, 4H), 6.61 (d, J = 8.1 Hz, 2H), 5.67 (d, J = 4.8 Hz, 1H), 5.31-4.91 (m, 2H), 4.44 (m, 2H), 4.20 (m, 1H), 4.00-3.61 (m, 6H), 3.18-2.74 (m, 7H), 1.86-1.64 (m, 3H), 1.38 (m, 3H), 1.20 (m, 6H), 0.93 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H);  
25   <sup>31</sup>P NMR (CDCl<sub>3</sub>) □ 19.1, 18; MS(ESI) 869 (M+Na). 30b (0.200 g, 33%, **GS 77425**, 1/1 diastereomeric mixture) as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.73 (dd, J = 8.7 Hz, J = 1.5 Hz, 2H), 7.36-7.16 (m, 5H), 7.09-7.00 (m, 4H), 6.53 (d, J = 8.7 Hz, 2H), 5.66 (d, J = 5.4 Hz, 1H), 5.06-4.91 (m, 2H), 4.40 (m, 2H), 4.20 (m, 1H), 4.00-3.60 (m, 6H), 3.14 (m, 3H), 3.00-2.65 (m, 6H), 1.86-1.60 (m, 3H), 1.35 (m, 3H), 1.20 (m, 9H), 0.92 (d, J = 6.6 Hz, 3H), 0.87  
30   (d, J = 6.6 Hz, 3H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) □ 19.0, 17.9. MS (ESI) 897 (M+Na).

#### Example 30

Synthesis of Bisamides 32: A solution of phosphonic acid 31 (100 mg, 0.15 mmol) and L-valine ethyl ester hydrochloride (108 mg, 0.60 mmol) was dissolved in pyridine (5 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of  $\text{Ph}_3\text{P}$  (117 mg, 0.45 mmol) and 2,2'-dipyridyl disulfide (98 mg, 0.45 mmol) in pyridine (1 mL) followed by addition of N,N-diisopropylethylamine (0.1 mL, 0.60 mmol). The reaction mixture was stirred at room temperature for two days. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel to give the bisamide (73 mg, 53%, GS 17389) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.72 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.1 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.1 Hz, 2H), 5.66 (d, J = 4.8 Hz, 1H), 5.05 (m, 1H), 4.95 (d, J = 8.7 Hz, 1H), 4.23-4.00 (m, 4H), 3.97-3.68 (m, 11H), 3.39-2.77 (m, 9H), 2.16 (m, 2H), 1.82-1.60 (m, 3H), 1.31-1.18 (m, 6H), 1.01-0.87 (m, 18H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  21.3; MS (ESI) 950 (M+Na).

#### Example 31

Triflate 34: To a solution of phenol 33 (2.00 g, 3.46 mmol) in THF (15 mL) and  $\text{CH}_2\text{Cl}_2$  (5 mL) was added N-phenyltrifluoromethanesulfonimide (1.40 g, 3.92 mmol) and cesium carbonate (1.40 g, 3.92 mmol). The reaction mixture was stirred at room temperature overnight and concentrated. The crude product was partitioned between  $\text{CH}_2\text{Cl}_2$  and saturated NaCl, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% MeOH/ $\text{CH}_2\text{Cl}_2$ ) to give the triflate (2.09 g, 85%) as a white solid.

#### Example 32

Aldehyde 35: To a suspension of triflate 34 (1.45 g, 2.05 mmol), palladium (II) acetate (46 mg, 0.20 mmol) and 1,3-bis(diphenylphosphino)propane (84 mg, 0.2 mmol) in DMF (8 mL) under CO atmosphere (balloon) was slowly added triethylamine (1.65 mL, 11.87 mmol) and triethylsilane (1.90 mL, 11.87 mmol). The reaction mixture was heated to 70°C under CO atmosphere (balloon) and stirred overnight. The solvent was concentrated under reduced pressure and partitioned between  $\text{CH}_2\text{Cl}_2$  and  $\text{H}_2\text{O}$ . The organic phase was dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude product was purified by column chromatography on silica gel (4% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the aldehyde (0.80 g, 66%) as a white solid.

Example 33

- Substituted Benzyl Alcohol 36: To a solution of aldehyde 35 (0.80g, 1.35 mmol) in THF (9 mL) and H<sub>2</sub>O (1 mL) at -10°C was added NaBH<sub>4</sub> (0.13 g, 3.39 mmol). The reaction mixture was stirred for 1 h at -10°C and the solvent was evaporated under reduced pressure. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and washed with NaHSO<sub>4</sub>, H<sub>2</sub>O, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (6% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the alcohol (0.56 g, 70%) as a white solid.

Example 34

- Substituted Benzyl Bromide 37: To a solution of alcohol 36 (77 mg, 0.13 mmol) in THF (1 mL) and CH<sub>2</sub>Cl<sub>2</sub> (1 mL) at 0°C was added triethylamine (0.027 mL, 0.20 mmol) and methanesulfonyl chloride (0.011 mL, 0.14 mmol). The reaction mixture was stirred at 0°C for 30 min and warmed to room temperature for 3 h. Lithium bromide (60 mg, 0.69 mmol) was added and stirred for 45 min. The reaction mixture was concentrated and the residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (2% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give the bromide (60 mg, 70%).

Example 35

- Diethylphosphonate 38: A solution of bromide 37 (49 mg, 0.075 mmol) and triethylphosphite (0.13 mL, 0.75 mmol) in toluene (1.5 mL) was heated to 120°C and stirred overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (6% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give the diethylphosphonate (35 mg, 66%, GS 191338) as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.72 (d, J = 8.7 Hz, 2H), 7.27-7.16 (m, 4H), 7.00 (d, J = 8.7 Hz, 2H), 5.66 (d, J = 5.1 Hz, 1H), 5.00 (m, 2H), 4.04-3.73 (m, 13H), 3.13-2.80 (m, 9H), 1.82-1.64 (m, 3H), 1.25 (t, J = 6.9 Hz, 6H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) □ 26.4; MS (ESI) 735 (M+Na).

Example 36

- N-tert-Butoxycarbonyl-O-benzyl-L-serine 39: To a solution of Boc-L-serine (15 g, 73.09 mmol) in DMF (300 mL) at 0°C was added NaH (6.43 g, 160.80 mmol, 60% in mineral oil) and stirred for 1.5 h at 0°C. After the addition of benzyl bromide (13.75 g, 80.40 mmol), the

reaction mixture was warmed to room temperature and stirred overnight. The solvent was evaporated under reduced pressure and the residue was dissolved in H<sub>2</sub>O. The crude product was partitioned between H<sub>2</sub>O and Et<sub>2</sub>O. The aqueous phase was acidified to pH<4 with 3 N HCl and extracted with EtOAc three times. The combined EtOAc solution was washed with  
5 H<sub>2</sub>O, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give the N-tert-butoxycarbonyl-O-benzyl-L-serine (17.27 g, 80%).

#### Example 37

Diazo Ketone 40: To a solution of N-tert-Butoxycarbonyl-O-benzyl-L-serine 39 (10 g, 33.86  
10 mmol) in dry THF (120 mL) at -15°C was added 4-methylmorpholine (3.8 mL, 34.54 mmol) followed by the slow addition of isobutylchloroformate (4.40 mL, 33.86 mmol). The reaction mixture was stirred for 30 min and diazomethane (~50 mmol, generated from 15 g Diazald according to Aldrichimica Acta 1983, 16, 3) in ether (~150 mL) was poured into the mixed anhydride solution. The reaction was stirred for 15 min and was then placed in an ice bath at  
15 0°C and stirred for 1 h. The reaction was allowed to warm to room temperature and stirred overnight. The solvent was evaporated under reduced pressure and the residue was dissolved in EtOAc, washed with water, saturated NaHCO<sub>3</sub>, saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated. The crude product was purified by column chromatography (EtOAc/hexane) to afford the diazo ketone (7.50 g, 69%) as a yellow oil.

#### Example 38

Chloroketone 41: To a suspension of diazoketone 40 (7.50 g, 23.48 mmol) in ether (160 mL) at 0°C was added 4N HCl in dioxane (5.87 mL, 23.48 mmol). The reaction mixture was stirred at 0°C for 1 h. The reaction solvent was evaporated under reduced pressure to give the  
25 chloroketone which was used directly without any further purification.

#### Example 39

Chloroalcohol 42: To a solution of chloroketone 41 (7.70 g, 23.48 mmol) in THF (90 mL) was added water (10 mL) and the solution was cooled to 0°C. A solution of NaBH<sub>4</sub> (2.67 g,  
30 70.45 mmol) in water (4 mL) was added dropwise over a period of 10 min. The mixture was stirred for 1 h at 0°C and saturated KHSO<sub>4</sub> was slowly added until the pH<4 followed by saturated NaCl. The organic phase was washed with saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The crude product was purified by column

chromatography on silica gel (1/4 EtOAc/hexane) to give the chloroalcohol (6.20 g, 80%) as a diastereomeric mixture.

#### Example 40

- 5 Epoxide 43: A solution of chloroalcohol 42 (6.20 g, 18.79 mmol) in EtOH (150 mL) was treated with 0.71 M KOH (1.27 g, 22.55 mmol) and the mixture was stirred at room temperature for 1 h. The reaction mixture was evaporated under reduced pressure and the residue was partitioned between EtOAc and water. The organic phase was washed with saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The
- 10 crude product was purified by column chromatography on silica gel (1/6 EtOAc/hexane) to afford the desired epoxide 43 (2.79 g, 45%) and a mixture of diastereomers 44 (1.43 g, 23%).

#### Example 41

- Sulfonamide 45: To a suspension of epoxide 43 (2.79 g, 8.46 mmol) in 2-propanol (30 mL)
- 15 was added isobutylamine (8.40 mL, 84.60 mmol) and the solution was refluxed for 1 h. The solution was evaporated under reduced pressure and the crude solid was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) and cooled to 0°C. Triethylamine (2.36 mL, 16.92 mmol) was added followed by the addition of 4-methoxybenzenesulfonyl chloride (1.75 g, 8.46 mmol). The solution was stirred for 40 min at 0°C, warmed to room temperature, and evaporated under reduced
- 20 pressure. The residue was partitioned between EtOAc and saturated NaHCO<sub>3</sub>. The organic phase was washed with saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The crude product was directly used without any further purification.

#### Example 42

- 25 Silyl Ether 46: A solution of sulfonamide 45 (5.10 g, 8.46 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was treated with triethylamine (4.7 mL, 33.82 mmol) and TMSOTf (3.88 mL, 16.91 mmol). The reaction mixture was stirred at room temperature for 1 h and partitioned between CH<sub>2</sub>Cl<sub>2</sub> and saturated NaHCO<sub>3</sub>. The aqueous phase was extracted twice with CH<sub>2</sub>Cl<sub>2</sub> and the combined organic extracts were washed with saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and
- 30 evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (1/6 EtOAc/hexane) to give the silyl ether (4.50 g, 84%) as a thick oil.

Example 43

Alcohol 47: To a solution of silyl ether 46 (4.5 g, 7.14 mmol) in MeOH (50 mL) was added 10% Pd/C (0.5 g). The suspension was stirred under H<sub>2</sub> atmosphere (balloon) at room temperature for 2 h. The reaction mixture was filtered through a plug of celite and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give the alcohol (3.40 g, 85%) as a white solid.

Example 44

Aldehyde 48: To a solution of alcohol 47 (0.60 g, 1.07 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (6 mL) at 0°C was added Dess Martin reagent (0.77 g, 1.82 mmol). The reaction mixture was stirred at 0°C for 3 h and partitioned between CH<sub>2</sub>Cl<sub>2</sub> and NaHCO<sub>3</sub>. The organic phase was washed with H<sub>2</sub>O, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (1/4 EtOAc/hexane) to give the aldehyde (0.45 g, 75%) as a pale yellow solid.

Example 45

Sulfonamide 50: To a suspension of epoxide (2.00 g, 5.41 mmol) in 2-propanol (20 mL) was added amine 49 (4.03 g, 16.23 mmol) (prepared in 3 steps starting from 4-(aminomethyl)piperidine according to Bioorg. Med. Chem. Lett., 2001, 11, 1261.). The reaction mixture was heated to 80°C and stirred for 1 h. The solution was evaporated under reduced pressure and the crude solid was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and cooled to 0°C. Triethylamine (4.53 mL, 32.46 mmol) was added followed by the addition of 4-methoxybenzenesulfonyl chloride (3.36 g, 16.23 mmol). The solution was stirred for 40 min at 0°C, warmed to room temperature for 1.5 h, and evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaHCO<sub>3</sub>. The organic phase was washed with saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the sulfonamide (2.50 g, 59%).

Example 46

Amine 51: A solution of sulfonamide 50 (2.50 g, 3.17 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (6 mL) at 0°C was treated with trifluoroacetic acid (3 mL). The solution was stirred for 30 min at 0°C and then



warmed to room temperature for an additional 1.5 h. Volatiles were evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5 N NaOH (2x), water (2x) and saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure to give the amine (1.96 g, 90%) which was used directly without any further purification.

#### Example 47

Carbamate 52: To a solution of amine 51 (1.96 g, 2.85 mmol) in CH<sub>3</sub>CN (15mL) at 0°C was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (0.84g, 2.85mmol, prepared according to Ghosh et al., J. Med. Chem. 1996, 39, 3278.) and 4-(dimethylamino)pyridine (0.70 g, 5.70 mmol). After stirring for 2 h at 0°C, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5N NaOH (2 x), 5% citric acid (2 x), saturated NaHCO<sub>3</sub>, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the carbamate (1.44 g, 60%) as a white solid.

### Example Section I

#### Example 1

Carbonate 2: To a solution of (R)-(+)-3-hydroxytetrahydrofuran (1.23 g, 14 mmol) in  
5 CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was added triethylamine (2.9 mL, 21 mmol) and bis(4-nitrophenyl)carbonate  
(4.7 g, 15.4 mmol). The reaction mixture was stirred at room temperature for 24 h and  
partitioned between CH<sub>2</sub>Cl<sub>2</sub> and saturated NaHCO<sub>3</sub>. The CH<sub>2</sub>Cl<sub>2</sub> layer was dried with  
Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column  
chromatography on silica gel (2/1-EtOAc/hexane) to give the carbonate (2.3 g, 65%) as a pale  
10 yellow oil which solidified upon standing.

#### Example 2

Carbamate 3: To a solution of 1 (0.385 g, 0.75 mmol) and 2 (0.210 g, 0.83 mmol) in CH<sub>3</sub>CN  
(7 mL) at room temperature was added N, N-diisopropylethylamine (0.16 mL, 0.90 mmol).  
15 The reaction mixture was stirred at room temperature for 44 h. The solvent was evaporated  
under reduced pressure. The crude product was dissolved in EtOAc and washed with  
saturated NaHCO<sub>3</sub>, brine, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product  
was purified by column chromatography on silica gel (1/1-EtOAc/hexane) to give the  
carbamate (0.322 g, 69%) as a white solid: mp 98-100°C (uncorrected).  
20

#### Example 3

Phenol 4: To a solution of 3 (0.31 g, 0.49 mmol) in EtOH (10 mL) and EtOAc (5 mL) was  
added 10% Pd/C (30 mg). The suspension was stirred under H<sub>2</sub> atmosphere (balloon) at  
room temperature for 15 h. The reaction mixture was filtered through a plug of celite. The  
25 filtrate was concentrated and dried under vacuum to give the phenol (0.265 g) in quantitative  
yield.

#### Example 4

Diethylphosphonate 5: To a solution of phenol 4 (100 mg, 0.19 mmol) in THF (3 mL) was  
30 added Cs<sub>2</sub>CO<sub>3</sub> (124 mg, 0.38 mmol) and triflate (85 mg, 0.29 mmol). The reaction mixture  
was stirred at room temperature for 4 h and the solvent was evaporated under reduced  
pressure. The residue was partitioned between EtOAc and saturated NaCl. The organic  
phase was dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The crude  
product was purified by column chromatography on silica gel (5% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to

give the diethylphosphonate (63 mg, 49%, GS 16573) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.65 (d,  $J = 8.7\text{ Hz}$ , 2H), 7.21 (d,  $J = 8.7\text{ Hz}$ , 2H), 6.95 (d,  $J = 9\text{ Hz}$ , 2H), 6.84 (d,  $J = 8.4\text{ Hz}$ , 2H), 5.06 (broad, s, 1H), 4.80 (d,  $J = 7.5\text{ Hz}$ , 1H), 4.19 (m, 6H), 3.83 (s, 3H), 3.80-3.70 (m, 6H), 3.09-2.72 (m, 6H), 2.00 (m, 1H), 1.79 (m, 2H), 1.32 (t,  $J = 7.5\text{ Hz}$ , 6H), 0.86 (d,  $J = 6.6\text{ Hz}$ , 3H), 0.83 (d,  $J = 6.6\text{ Hz}$ , 3H);  $^{31}\text{P}$  NMR  $\delta$  17.8.

#### Example 5

Dibenzylphosphonate 6: To a solution of phenol 4 (100 mg, 0.19 mmol) in THF (3 mL) was added  $\text{Cs}_2\text{CO}_3$  (137 mg, 0.42 mmol) and triflate (165 mg, 0.39 mmol). The reaction mixture was stirred at room temperature for 6 h and the solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried with  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (5% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the dibenzylphosphonate (130 mg, 84%, GS 16574) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.65 (d,  $J = 9\text{ Hz}$ , 2H), 7.30 (m, 10H), 7.08 (d,  $J = 8.4\text{ Hz}$ , 2H), 6.94 (d,  $J = 9\text{ Hz}$ , 2H), 6.77 (d,  $J = 8.7\text{ Hz}$ , 2H), 5.16-5.04 (m, 5H), 4.80 (d,  $J = 8.1\text{ Hz}$ , 1H), 4.16 (d,  $J = 10.2\text{ Hz}$ , 2H), 3.82 (s, 3H), 3.75-3.71 (m, 6H), 3.10-2.72 (m, 6H), 2.00 (m, 1H), 1.79 (m, 2H), 0.86 (d,  $J = 6.6\text{ Hz}$ , 3H), 0.83 (d,  $J = 6.6\text{ Hz}$ , 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  18.8.

#### Example 6

Phosphonic Acid 7: To a solution of 6 (66 mg, 0.08 mmol) in EtOH (3 mL) was added 10% Pd/C (12 mg). The suspension was stirred under  $\text{H}_2$  atmosphere (balloon) at room temperature for 15 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated under reduced pressure and triturated with EtOAc to give the phosphonic acid (40 mg, 78%, GS 16575) as a white solid.

#### Example 7

Carbonate 8: To a solution of (S)-(+)-3-hydroxytetrahydrofuran (2 g, 22.7 mmol) in  $\text{CH}_3\text{CN}$  (50 mL) was added triethylamine (6.75 mL, 48.4 mmol) and N,N'-disuccinimidyl carbonate (6.4 g, 25 mmol). The reaction mixture was stirred at room temperature for 5 h and concentrated under reduced pressure. The residue was partitioned between EtOAc and  $\text{H}_2\text{O}$ . The organic phase was dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc as eluant)

followed by recrystallization (EtOAc/hexane) to give the carbonate (2.3 g, 44%) as a white solid.

#### Example 8

- 5 Carbamate 9: To a solution of 1 (0.218 g, 0.42 mmol) and 8 (0.12 g, 0.53 mmol) in CH<sub>3</sub>CN (3 mL) at room temperature was added N, N-diisopropylethylamine (0.11 mL, 0.63 mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated and the residue was partitioned between EtOAc and saturated NaHCO<sub>3</sub>. The organic phase was washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product
- 10 was purified by column chromatography on silica gel (1/1-EtOAc/hexane) to give the carbamate (0.176 g, 66%) as a white solid.

#### Example 9

- Phenol 10: To a solution of 9 (0.176 g, 0.28 mmol) in EtOH (10 mL) was added 10% Pd/C
- 15 (20 mg). The suspension was stirred under H<sub>2</sub> atmosphere (balloon) at room temperature for 4 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phenol (0.151 g, **GS 10**) in quantitative yield.

#### Example 10

- 20 Diethylphosphonate 11: To a solution of phenol 10 (60 mg, 0.11 mmol) in THF (3 mL) was added Cs<sub>2</sub>CO<sub>3</sub> (72 mg, 0.22 mmol) and triflate (66 mg, 0.22 mmol). The reaction mixture was stirred at room temperature for 4 h and the solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The crude
- 25 product was purified by column chromatography on silica gel (5% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the diethylphosphonate (38 mg, 49%, **GS 11**) as a white solid.

## Example Section J

### Example 1

Triflate 1: To a solution of A (4 g, 6.9 mmol) in THF (30 mL) and CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was  
5 added Cs<sub>2</sub>CO<sub>3</sub> (2.7 g, 8 mmol) and N-phenyltrifluoromethanesulfonimide (2.8 g, 8.0 mmol)  
and stirred at room temperature for 16 h. The reaction mixture was concentrated under  
reduced pressure. The residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and saturated brine twice.  
The organic phase was dried over sodium sulfate and used for next reaction without further  
purification.

10

### Example 2

Aldehyde 2: A solution of crude above triflate 1 (~6.9 mmol) in DMF (20 mL) was degassed  
(high vacuum for 5 min, argon purge, repeat 3 times). To this solution were quickly added  
Pd(OAc)<sub>2</sub> (120 mg, 266 μmol) and bis(diphenylphosphino-propane) (dppp, 220 mg, 266  
15 μmol), and heated to 70°C. To this reaction mixture was rapidly introduced carbon  
monoxide, and stirred at room temperature under an atmospheric pressure of carbon  
monoxide, followed by slow addition of TEA (5.4 mL, 38 mmol) and triethylsilane (3 mL, 18  
mmol). The resultant mixture was stirred at 70°C for 16 h, then cooled to room temperature,  
concentrated under reduced pressure, partitioned between CH<sub>2</sub>Cl<sub>2</sub> and saturated brine. The  
20 organic phase was concentrated under reduced pressure and purified on silica gel column to  
afford aldehyde 2 (2.1 g, 51%) as white solid.

### Example 3

Compounds 3a-3e: Representative Procedure, 3c: A solution of aldehyde 2 (0.35 g, 0.59  
25 mmol), L-alanine isopropyl ester hydrochloride (0.2 g, 1.18 mmol), glacial acetic acid (0.21  
g, 3.5 mmol) in 1,2-dichloroethane (10 mL) was stirred at room temperature for 16 h,  
followed by addition of sodium cyanoborohydride (0.22 g, 3.5 mmol) and methanol (0.5 mL).  
The resulting solution was stirred at room temperature for one h. The reaction mixture was  
washed with sodium bicarbonate solution, saturated brine, and chromatographed on silica gel  
30 to afford 3c (0.17 g, 40%). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.72 (d, 2H), 7.26 (d, 2H), 7.20 (d, 2H), 7.0  
(d, 2H), 5.65 (d, 1H), 4.90-5.30 (m, 3H), 3.53-4.0 (m overlapping s, 13H), 3.31 (q, 1H),  
2.70-3.20 (m, 7H), 1.50-1.85 (m, 3H), 1.25-1.31 (m, 9H), 0.92 (d, 3H), 0.88 (d, 3H). MS: 706  
(M + 1).

Compound	R <sub>1</sub>	R <sub>2</sub>	Amino Acid
3a	Me	Me	Ala
3b	Me	Et	Ala
3c	Me	iPr	Ala
3d	Me	Bn	Ala
3e	iPr	Et	Val

Example 4

Sulfonamide 1: To a solution of crude amine A (1 g, 3 mmol) in CH<sub>2</sub>Cl<sub>2</sub> was added TEA  
 5 (0.6 g, 5.9 mmol) and 3-methoxybenzenesulfonyl chloride (0.6 g, 3 mmol). The resulting solution was stirred at room temperature for 5 h, and evaporated under reduced pressure. The residue was chromatographed on silica gel to afford sulfonamide 1 (1.0 g, 67%).

Example 5

10 Amine 2: To a 0°C cold solution of sulfonamide 1 (0.85 g, 1.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) was treated with BBr<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> (10 mL of 1 M solution, 10 mmol). The solution was stirred at 0°C 10 min and then warmed to room temperature and stirred for 1.5 h. The reaction mixture was quenched with CH<sub>3</sub>OH, concentrated under reduced pressure, azeotroped with CH<sub>3</sub>CN three times. The crude amine 2 was used for next reaction without further  
 15 purification.

Example 6

Carbamate 3: A solution of crude amine 2 (0.83 mmol) in CH<sub>3</sub>CN (20 mL) and was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (245 mg, 0.83  
 20 mmol, prepared according to Ghosh et al., J. Med. Chem. 1996, 39, 3278.) and N,N-dimethylaminopyridine (202 mg, 1.7 mmol). After stirring for 16 h at room temperature, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and saturated NaHCO<sub>3</sub> three times. The organic phase was evaporated under reduced pressure. The residue was purified by chromatography on silica gel affording  
 25 the carbamate 3 (150 mg, 33%) as a solid.

Example 7

Diethylphosphonate 4: To a solution of carbamate 3 (30 mg, 54  $\mu\text{mol}$ ) in THF (5 mL) was added  $\text{Cs}_2\text{CO}_3$  (54 mg, 164  $\mu\text{mol}$ ) and triflate # (33 mg, 109  $\mu\text{mol}$ ). After stirring the reaction mixture for 30 min at room temperature, additional  $\text{Cs}_2\text{CO}_3$  (20 mg, 61  $\mu\text{mol}$ ) and triflate (15 mg, 50  $\mu\text{mol}$ ) were added and the mixture was stirred for 1 more hour. The reaction mixture was evaporated under reduced pressure and the residue was partitioned between  $\text{CH}_2\text{Cl}_2$  and water. The organic phase was dried ( $\text{Na}_2\text{SO}_4$ ), filtered and evaporated under reduced pressure. The crude product was chromatographed on silica gel and repurified by HPLC (50%  $\text{CH}_3\text{CN}$ -50%  $\text{H}_2\text{O}$  on C18 column) to give the diethylphosphonate 4 (15 mg, 39%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.45 (m, 3H), 7.17-7.30 (m, 6H), 5.64 (d, 1H), 5.10 (d, 1H), 5.02 (q, 1H), 4.36 (d, 2H), 4.18-4.29 (2 q overlap, 4H), 3.60-3.98 (m, 7H), 2.70-3.10 (m, 7H), 1.80-1.90 (m, 1H), 1.44-1.70 (m, 2H +  $\text{H}_2\text{O}$ ), 1.38 (t, 6H), 0.94 (d, 3H), 0.90 (d, 3H).  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ ): 18.7 ppm; MS (ESI) 699 (M + H).

#### Example 8

Dibenzylphosphonate 5: To a solution of carbamate 3 (100 mg, 182  $\mu\text{mol}$ ) in THF (10 mL) was added  $\text{Cs}_2\text{CO}_3$  (180 mg, 550  $\mu\text{mol}$ ) and dibenzylhydroxymethyl phosphonate triflate, Section A, Scheme 2, Compound 9, (150 mg, 360  $\mu\text{mol}$ ). After stirring the reaction mixture for 1 h at room temperature, the reaction mixture was evaporated under reduced pressure and the residue was partitioned between  $\text{CH}_2\text{Cl}_2$  and water. The organic phase was dried ( $\text{Na}_2\text{SO}_4$ ), filtered and evaporated under reduced pressure. The residue was purified by HPLC (50%  $\text{CH}_3\text{CN}$ -50%  $\text{H}_2\text{O}$  on C18 column) to give the dibenzylphosphonate 5 (110 mg, 72%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.41 (d, 2H), 7.35 (s, 10 H), 7.17-7.30 (m, 6H), 7.09-7.11 (m, 1H), 5.64 (d, 1H), 4.90-5.15 (m, 6H), 4.26 (d, 2H), 3.81-3.95 (m, 4H), 3.64-3.70 (m, 2H), 2.85-3.25 (m, 7H), 1.80-1.95 (m, 1H), 1.35-1.50 (m, 1H), 0.94 (d, 3H), 0.91 (d, 3H).  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.4 ppm; MS (ESI): 845 (M + Na), 1666 (2M + Na).

#### Example 9

Phosphonic acid 6: A solution of dibenzylphosphonate 5 (85 mg, 0.1 mmol) was dissolved in MeOH (10 mL) treated with 10% Pd/C (40 mg) and stirred under  $\text{H}_2$  atmosphere (balloon) overnight. The reaction was purged with  $\text{N}_2$ , and the catalyst was removed by filtration through celite. The filtrate was evaporated under reduced pressure to afford phosphonic acid 6 (67 mg, quantitatively).  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  7.40-7.55 (m, 3H), 7.10-7.35 (m, 6H), 5.57

(d, 1H), 4.32 (d, 2H), 3.90-3.95 (m, 1H), 3.64-3.78 (m, 5H), 3.47 (m, 1H), 2.85-3.31 (m, 5H), 2.50-2.60 (m, 1H), 2.00-2.06 (m, 1H), 1.46-1.60 (m, 1H), 1.30-1.34 (m, 1H), 0.9 (d, 3H), 0.90 (d, 3H). <sup>31</sup>P NMR (CD<sub>3</sub>OD): 16.60 ppm; MS (ESI): 641 (M - H).

#### 5 Example 10

Sulfonamide 1: To a solution of crude amine A (0.67 g, 2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was added TEA (0.24 g, 24 mmol) and crude 3-acetoxy-4-methoxybenzenesulfonyl chloride (0.58 g, 2.1 mmol), was prepared according to Kratzl et al., Monatsh. Chem. 1952, 83, 1042-1043), and the solution was stirred at room temperature for 4 h, and evaporated under reduced  
10 pressure. The residue was chromatographed on silica gel to afford sulfonamide 1 (0.64 g, 54%). MS: 587 (M + Na), 1150 (2M + Na)

Phenol 2: Sulfonamide 1 (0.64 g, 1.1 mmol) was treated with saturated NH<sub>3</sub> in MeOH (15 mL) at room temperature for 15 min., then evaporated under reduced pressure. The residue  
15 was purified on silica gel column to afford phenol 2 (0.57 g, 96%).

#### Example 11

Dibenzylphosphonate 3a: To a solution of phenol 2 (0.3 g, 0.57 mmol) in THF (8 mL) was added Cs<sub>2</sub>CO<sub>3</sub> (0.55 g, 1.7 mmol) ) and dibenzylhydroxymethyl phosphonate triflate (0.5 g, 1.1 mmol). After stirring the reaction mixture for 1 h at room temperature, the reaction  
20 mixture was quenched with water and partitioned between CH<sub>2</sub>Cl<sub>2</sub> and saturated ammonium chloride aqueous solution. The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated under reduced pressure. The residue was chromatographed on silica gel (40% EtOAc/ 60% hexane) to give the dibenzylphosphonate 3a (0.36 g, 82%). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.20-7.40  
25 (m, 17H), 6.91 (d, 1H), 5.10-5.25 (2 q(ab) overlap, 4H), 4.58-4.70 (m, 1H), 4.34 (d, 2H), 3.66-3.87 (m + s, 5H), 2.85-3.25 (m, 6H), 1.80-1.95 (m, 1H), 1.58 (s, 9H), 0.86-0.92 (2d, 6H).

#### Example 12

Diethylphosphonate 3b: To a solution of phenol 2 (0.15 g, 0.28 mmol) in THF (4 mL) was added Cs<sub>2</sub>CO<sub>3</sub> (0.3 g, 0.92 mmol) ) and diethylhydroxymethyl phosphonate triflate (0.4 g, 1.3 mmol). After stirring the reaction mixture for 1 h at room temperature, the reaction mixture was quenched with water and partitioned between CH<sub>2</sub>Cl<sub>2</sub> and saturated NaHCO<sub>3</sub> aqueous



solution. The organic phase was dried ( $\text{Na}_2\text{SO}_4$ ), filtered and evaporated under reduced pressure. The residue was chromatographed on silica gel (1%  $\text{CH}_3\text{OH}-\text{CH}_2\text{Cl}_2$ ) to give the diethylphosphonate 3b (0.14 g, 73%).

5 Example 13

Amine 4a: To a solution of 3a (0.35 g, 0.44 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) was treated with TFA (0.75 g, 6.6 mmol) at room temperature for 2 h. The reaction was evaporated under reduced pressure, azeotroped with  $\text{CH}_3\text{CN}$  twice, dried to afford crude amine 4a. This crude 4a was used for next reaction without further purification.

10

Example 14

Amine 4b: To a solution of 3b (60 mg, 89  $\mu\text{mol}$ ) in  $\text{CH}_2\text{Cl}_2$  (1 mL) was treated with TFA (0.1 mL, 1.2 mmol) at room temperature for 2 h. The reaction was evaporated under reduced pressure, azeotroped with  $\text{CH}_3\text{CN}$  twice, dried to afford crude amine 4b (68 mg). This crude

15

Example 15

Carbamate 5a: An ice-cold solution of crude amine 4a (0.44 mmol) in  $\text{CH}_3\text{CN}$  (10 mL) and was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-b]furan-2-yl 4-nitrophenyl carbonate (120 mg, 0.4 mmol) and N,N-dimethylaminopyridine (DMAP, 110 mg, 0.88 mmol). After 4 h, more DMAP (0.55 g, 4.4 mmol) was added to the reaction mixture. After stirring for 1.5 h at room temperature, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between  $\text{CH}_2\text{Cl}_2$  and saturated  $\text{NaHCO}_3$ . The organic phase was evaporated under reduced pressure. The residue was purified by chromatography on silica

20 gel affording the crude carbamate 5a (220 mg) containing some p-nitrophenol. The crude 5a was repurified by HPLC (50%  $\text{CH}_3\text{CN}$  /50%  $\text{H}_2\text{O}$ ) to afford pure carbamate 5a (176 mg, 46%, 2 steps).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.20-7.36 (m, 1H), 6.94 (d, 1H), 5.64 (d, 1H), 5.10-5.25 (2 q(ab) overlap, 4H), 4.90-5.10 (m, 1H), 4.90 (d, 1H), 4.34 (d, 2H), 3.82-3.91 (m + s, 6H), 3.63-3.70 (m, 3H), 2.79-3.30 (m, 7H), 1.80-1.90 (m, 1H), 1.40-1.50 (m, 1H), 0.94 (d, 3H),

30 0.89 (d, 3H).  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ ): 17.2 ppm.

Example 16

Carbamate 5b: An ice-cold solution of crude amine 4b (89  $\mu$ mol) in  $\text{CH}_3\text{CN}$  (5 mL) and was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (26mg, 89  $\mu$ mol) and *N,N*-dimethylaminopyridine (DMAP, 22 mg, 0.17 mmol). After 1 h at 0°C, more DMAP (10 mg, 82  $\mu$ mol) was added to the reaction mixture. After stirring for 2 h at room temperature, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between  $\text{CH}_2\text{Cl}_2$  and saturated  $\text{NaHCO}_3$ . The organic phase was evaporated under reduced pressure. The residue was purified by HPLC (C18 column, 45%  $\text{CH}_3\text{CN}/55\%$   $\text{H}_2\text{O}$ ) to afford pure carbamate 5b (18.8 mg, 29%, 3 steps).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.38 (d, 2H), 7.20-7.36 (m, 6H), 7.0 (d, 1H), 5.64 (d, 1H), 4.96-5.03 (m, 2H), 4.39 (d, 2H), 4.20-4.31 (2q overlap, 4H) 3.80-4.00 ((s overlap with m, 7H), 3.60-3.73 (m, 2H), 3.64-3.70 (m, 2H), 2.85-3.30 (m, 7H), 1.80-1.95 (m, 1H), 1.55-1.75 (m, 1H), 1.35-1.50 (s overlap with m, 7H), 0.94 (d, 3H), 0.88 (d, 3H).  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ ): 18.1ppm.

#### Example 17

Phosphonic acid 6: A solution of dibenzylphosphonate 5a (50 mg, 58  $\mu$ mol) was dissolved in MeOH (5 mL) and EtOAc (3 mL) and treated with 10% Pd/C (25 mg) and was stirred at room temperature under  $\text{H}_2$  atmosphere (balloon) for 8 h. The catalyst was filtered off. The filtrate was concentrated and redissolved in MeOH (5 mL), treated with 10% Pd/C (25 mg) and was stirred at room temperature under  $\text{H}_2$  atmosphere (balloon) overnight. The catalyst was filtered off. The filtrate was evaporated under reduced pressure to afford phosphonic acid 6 (38 mg, quantitatively).  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  7.42 (m, 1H), 7.36 (s, 1H), 7.10-7.25 (m, 6H), 5.58 7 (d, 1H), 4.32 (d, 2H), 3.90 (s, 3H), 3.60-3.80 (m, 6H), 3.38 (d, 1H), 2.85-3.25 (m, 5H), 2.50-2.60 (m, 1H), 1.95-2.06 (m, 1H), 1.46-1.60 (m, 1H), 1.30-1.40 (m, 1H), 0.93(d, 3H), 0.89 (d, 3H).  $^{31}\text{P}$  NMR ( $\text{CD}_3\text{OD}$ ): 14.8 ppm; MS (ESI): 671 (M - H).

#### Example 18

Amine 7: To a 0°C cold solution of diethylphosphonate 3b (80 mg, 0.118 mmol) in  $\text{CH}_2\text{Cl}_2$  was treated with  $\text{BBR}_3$  in  $\text{CH}_2\text{Cl}_2$  (0.1 mL of 1 M solution, 1 mmol). The solution was stirred at 0°C 10 min and then warmed to room temperature and stirred for 3 h. The reaction mixture was concentrated under reduced pressure. The residue was redissolved in  $\text{CH}_2\text{Cl}_2$  (containing some  $\text{CH}_3\text{OH}$ , concentrated, azeotroped with  $\text{CH}_3\text{CN}$  three times. The crude amine 7 was used for next reaction without further purification.

Example 19

Carbamate 8: An ice-cold solution of crude amine 7 (0.118 mmol) in CH<sub>3</sub>CN (5 mL) and was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (35 mg, 0.118 mmol) and N,N-dimethylaminopyridine (29 mg, 0.24mmol), warmed to room temperature. After stirring for 1 h at room temperature, more DMAP (20 mg, 0.16 mmol) was added to reaction mixture. After 2 h stirred at room temperature, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and saturated NaHCO<sub>3</sub>. The organic phase was evaporated under reduced pressure. The residue was purified by HPLC on C18 (CH<sub>3</sub>CN-55%H<sub>2</sub>O) to afford the desired carbamate 8 (11.4 mg, 13.4%) as an off-white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.20-7.40 (m, 7H), 7.00 (d, 1H), 5.64 (d, 1H), 5.00-5.31 (m, 2H), 4.35 (d, 2H), 4.19-4.30 (2q overlap, 4H), 3.80-4.00 (m, 4H), 3.68-3.74 (m, 2H), 3.08-3.20 (m, 3H), 2.75-3.00 (m, 4H), 1.80-1.90 (m, 1H), 1.55-1.75 (m, 1H), 1.38 (t, 6H), 0.91 (2d overlap, 6H). <sup>31</sup>P NMR (CD<sub>3</sub>OD): δ19.5 ppm.

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## Example Section K

### Example 1

Monophenyl-monolactate 3: A mixture of monoacid 1 (0.500 g, 0.7 mmol), alcohol 2 (0.276 g, 2.09 mmol) and dicyclohexylcarbodiimide (0.431 g, 2.09 mmol) in dry pyridine (4 mL) was placed into a 70°C oil bath and heated for two hours. The reaction was monitored by TLC assay (SiO<sub>2</sub>, 70% ethyl acetate in hexanes as eluent, product R<sub>f</sub> = 0.68, visualization by UV). The reaction contents were cooled to ambient temperature with the aid of a cool bath and diluted with dichloromethane (25 mL). TLC assay may show presence of starting material. The diluted reaction mixture was filtered to remove solids. The filtrate was then cooled to 0°C and charged with 0.1 N HCl (10 mL). The pH 4 mixture was stirred for 10 minutes and poured into separatory funnel to allow the layers to separate. The lower organic layer was collected and dried over sodium sulfate. The drying agent was filtered off and the filtrate concentrated to an oil via rotary evaporator (< 30°C warm bath). The crude product oil was purified on pretreated silica gel (deactivated using 10% methanol in dichloromethane followed by rinse with 60% ethyl acetate in dichloromethane). The product was eluted with 60% ethyl acetate in dichloromethane to afford the product monophenyl-monolactate 3 as a white foam (0.497 g, 86% yield). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.75 (d, 2H), 7.40-7.00 (m, 14H), 5.65 (d, 1H), 5.20-4.90 (m, 4H), 4.70 (d, 1H), 4.55-4.50 (m, 1H), 4.00-3.80 (m, 4H), 3.80-3.60 (m, 3H), 3.25-2.75 (m, 7H), 1.50 (d, 3H), 1.30-1.20 (m, 7H), 0.95 (d, 3H), 0.85 (d, 3H). <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 16.2, 13.9.

### Example 2

Monophenyl-monoamidate 5: A mixture of monoacid 1 (0.500 g, 0.70 mmol), amine hydrochloride 4 (0.467 g, 2.78 mmol) and dicyclohexylcarbodiimide (0.862 g, 4.18 mmol) in dry pyridine (8 mL) was placed into a 60°C oil bath, and heated for one hour (at this temperature, product degrades if heating continues beyond this point). The reaction was monitored by TLC assay (SiO<sub>2</sub>, 70% ethyl acetate in hexanes as eluent, product R<sub>f</sub> = 0.39, visualization by UV). The contents were cooled to ambient temperature and diluted with ethyl acetate (15 mL) to precipitate a white solid. The mixture was filtered to remove solids and the filtrate was concentrated via rotary evaporator to an oil. The oil was diluted with dichloromethane (20 mL) and washed with 0.1 N HCl (2 x 20 mL), water (1 x 20 mL) and dilute sodium bicarbonate (1 x 20 mL). The organic layer was dried over sodium sulfate,

filtered, and concentrated to an oil via rotary evaporator. The crude product oil was dissolved in dichloromethane (10 mL). Hexane was slowly charged to the stirring solution until cloudiness persisted. The cloudy mixture was stirred for a few minutes until TLC assay showed that the dichloromethane/hexane layer contained no product. The

5 dichloromethane/hexanes layer was decanted and the solid was further purified on silica gel first pretreated with 10% methanol in ethyl acetate and rinsed with 50% ethyl acetate in hexanes. The product 5 was eluted with 50% ethyl acetate in hexanes to afford a white foam (0.255 g, 44% yield) upon removal of solvents.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.75 (d, 2H), 7.40-7.15 (m, 10H), 7.15-7.00 (t, 2H), 5.65 (d, 1H), 5.10-4.90 (m, 3H), 4.50-4.35 (m, 2H), 4.25-4.10 (m, 1H), 4.00-3.60 (m, 8H), 3.20-2.75 (m, 7H), 1.40-1.20 (m, 11H), 0.95 (d, 3H), 0.85 (d, 10 3H).  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.1, 18.0.

### Example 3

Bisamidate 8: A solution of triphenylphosphine (1.71 g, 6.54 mmol) and aldrithiol (1.44 g, 15 6.54 mmol) in dry pyridine (5 mL), stirred for at least 20 minutes at room temperature, was charged into a solution of diacid 6 (1.20 g, 1.87 mmol) and amine hydrochloride 7 (1.30 g, 7.47 mmol) in dry pyridine (10 mL). Diisopropylethylamine (0.97 g, 7.48 mmol) was then added to this combined solution and the contents were stirred at room temperature for 20 hours. The reaction was monitored by TLC assay ( $\text{SiO}_2$ , 5:5:1 ethyl 20 acetate/hexanes/methanol as eluent, product  $R_f$  = 0.29, visualization by UV). The reaction mixture was concentrated via rotary evaporator and dissolved in dichloromethane (50 mL). Brine (25 mL) was charged to wash the organic layer. The aqueous layer was back extracted with dichloromethane (1 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated via rotary evaporator to afford an oil. The crude product oil 25 was purified on silica gel using 4% isopropanol in dichloromethane as eluent. The combined fractions containing the product may have residual amine contamination. If so, the fractions were concentrated via rotary evaporator and further purified by silica gel chromatography using a gradient of 1:1 ethyl acetate/hexanes to 5:5:1 ethyl acetate/hexanes/methanol solution as eluent to afford the product 8 as a foam (0.500 g, 30% yield).

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### Example 4

Diacid 6: A solution of dibenzylphosphonate 9 (8.0 g, 9.72 mmol) in ethanol (160 mL) and ethyl acetate (65 mL) under a nitrogen atmosphere and at room temperature was charged 10%

Pd/C (1.60 g, 20 wt%). The mixture was stirred and evacuated by vacuum and purged with hydrogen several times. The contents were then placed under atmospheric pressure of hydrogen via a balloon. The reaction was monitored by TLC assay (SiO<sub>2</sub>, 7:2.5:0.5 dichloromethane/methanol/ammonium hydroxide as eluent, product R<sub>f</sub> = 0.05, visualization by UV) and was judged complete in 4 to 5 hours. The reaction mixture was filtered through a pad of celite to remove Pd/C and the filter cake rinsed with ethanol/ethyl acetate mixture (50 mL). The filtrate was concentrated via rotary evaporation followed by several co-evaporations using ethyl acetate (3 x 50 mL) to remove ethanol. The semi-solid diacid 6, free of ethanol, was carried forward to the next step without purification.

#### Example 5

Diphenylphosphonate 10: To a solution of diacid 6 (5.6 g, 8.71 mmol) in pyridine (58 mL) at room temperature was charged phenol (5.95 g, 63.1 mmol). To this mixture, while stirring, was charged dicyclohexylcarbodiimide (7.45 g, 36.0 mmol). The resulting cloudy, yellow mixture was placed in a 70-80°C oil bath. The reaction was monitored by TLC assay (SiO<sub>2</sub>, 7:2.5:0.5 dichloromethane/methanol/ammonium hydroxide as eluent, diacid R<sub>f</sub> = 0.05, visualization by UV for the disappearance of starting material. SiO<sub>2</sub>, 60% ethyl acetate in hexanes as eluent, diphenyl R<sub>f</sub> = 0.40, visualization by UV) and was judged complete in 2 hours. To the reaction mixture was charged isopropyl acetate (60 mL) to produce a white precipitation. The slurry was filtered through a pad of celite to remove the white precipitate and the filter cake rinsed with isopropyl acetate (25 mL). The filtrate was concentrated via rotary evaporator. To the resulting yellow oil was charged a premixed solution of water (58 mL) and 1N HCl (55 mL) followed by isopropyl acetate (145 mL). The mixture was stirred for one hour in an ice bath. After separating the layers, the aqueous layer was back extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated via rotary evaporator. The crude product oil was purified by silica gel column chromatography using 50% ethyl acetate in hexanes as eluent to afford the product 10 as a white foam (3.52 g, 51% yield). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.75 (d, 2H), 7.40-7.20 (m, 15H), 7.10 (d, 2H), 5.65 (d, 1H), 5.10-4.90 (m, 2H), 4.65 (d, 2H), 4.00-3.80 (m, 4H), 3.75-3.65 (m, 3H), 3.25-2.75 (m, 7H), 1.90-1.75 (m, 1H), 1.70-1.60 (m, 1H), 1.50-1.40 (m, 1H), 0.90 (d, 3H), 0.85 (d, 3H). <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 10.9.

#### Example 6

Monophenyl 1: To a solution of diphenyl 10 (3.40 g, 4.28 mmol) in acetonitrile (170 mL) at 0°C was charged 1N sodium hydroxide (4.28 mL). The reaction was monitored by TLC assay (SiO<sub>2</sub>, 7:2.5:0.5 dichloromethane/methanol/ammonium hydroxide as eluent, diphenyl R<sub>f</sub> = 0.65, visualization by UV for the disappearance of starting material. Product monophenyl R<sub>f</sub> = 0.80, visualization by UV). Additional 1N NaOH was added (if necessary) until the reaction was judged complete. To the reaction contents at 0°C was charged Dowex H<sup>+</sup> (Dowex 50WX8-200) (4.42 g) and stirred for 30 minutes at which time the pH of the mixture reached pH 1 (monitored by pH paper). The mixture was filtered to remove the Dowex resin and the filtrate was concentrated via rotary evaporation (water bath < 40°C). The resulting solution was co-evaporated with toluene to remove water (3 x 50 mL). The white foam was dissolved in ethyl acetate (8 mL) followed by slow addition of hexanes (16 mL) over 30 minutes to induce precipitation. A premixed solution of 2:1 hexanes/ethyl acetate solution (39 mL) was charged to the precipitated material and stirred. The product 1 was filtered and rinsed with premixed solution of 2:1 hexanes/ethyl acetate solution (75 mL) and dried under vacuum to afford a white powder (2.84 g, 92% yield). <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.80 (d, 2H), 7.40-7.30 (m, 2H), 7.20-7.15 (m, 11H), 5.55 (d, 1H), 4.50 (d, 2H), 3.95-3.85 (m, 1H), 3.80-3.60 (m, 5H), 3.45 (bd, 1H), 3.25-3.15 (m, 2H), 3.00-2.80 (m, 3H), 2.60-2.45 (m, 1H), 2.10-1.95 (m, 2H), 1.85-1.60 (m, 2H), 1.50-1.40 (m, 1H), 1.40-1.30 (m, 1H), 0.95 (d, 3H), 0.85 (d, 3H). <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 13.8. The monophenyl product 1 is sensitive to silica gel. On contact with silica gel 1 converts to an unknown compound possessing <sup>31</sup>P NMR chemical shift of 8 ppm. However, the desired monophenyl product 1 can be regenerated by treatment of the unknown compound with 2.5 M NaOH in acetonitrile at 0°C for one hour followed by Dowex H<sup>+</sup> treatment as described above.

#### 25 Example 7

Dibenzylphosphonate 9: To a solution of phenol 11 (6.45 g, 11.8 mmol) in tetrahydrofuran (161 mL) at room temperature was charged triflate reagent 12 (6.48 g, 15.3 mmol). Cesium carbonate (11.5 g, 35.3 mmol) was added and the mixture was stirred and monitored by TLC assay (SiO<sub>2</sub>, 5% methanol in dichloromethane as eluent, dibenzyl product R<sub>f</sub> = 0.26, visualization by UV or ninhydrin stain and heat). Additional Cs<sub>2</sub>CO<sub>3</sub> was added until the reaction was judged complete. To the reaction contents was charged water (160 mL) and the mixture extracted with ethyl acetate (2 x 160 mL). The combined organic layer was dried over sodium sulfate, filtered, and concentrated via rotary evaporator to afford a viscous oil.

The crude oil was purified by silica gel column chromatography using a gradient of 100% dichloromethane to 1% methanol in dichloromethane to afford product 9 as a white foam (8.68 g, 90% yield).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.75 (d, 2H), 7.40-7.20 (m, 16H), 6.95 (d, 2H), 5.65 (d, 1H), 5.20-4.90 (m, 6H), 4.25 (d, 2H), 4.00-3.80 (m, 4H), 3.75-3.65 (m, 3H), 3.20-2.75 (m, 7H), 1.90-1.75 (m, 1H), 1.30-1.20 (m, 1H), 0.90 (d, 3H), 0.85 (d, 3H).  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.1.

#### Example 7a

Hydroxyphenylsulfonamide 14: To a solution of methoxyphenylsulfonamide 13 (35.9 g, 70.8 mmol) in dichloromethane (3.5 L) at  $0^\circ\text{C}$  was charged boron tribromide (1M in DCM, 40.1 mL, 425 mmol). The reaction content was allowed to warm to room temperature, stirred over two hours, and monitored by TLC assay ( $\text{SiO}_2$ , 10% methanol in dichloromethane as eluent, dibenzyl product  $R_f = 0.16$ , visualization by UV). To the contents at  $0^\circ\text{C}$  was slowly charged propylene oxide (82 g, 1.42 mmol). Methanol (200 mL) was added and the reaction mixture was concentrated via rotary evaporator to afford a viscous oil. The crude product mixture was purified by silica gel column chromatography using 10% methanol in dichloromethane to afford the product 14 as a foam (22 g, 80% yield).  $^1\text{H}$  NMR (DMSO)  $\delta$  7.60 (d, 2H), 7.30-7.20 (m, 5H), 6.95 (d, 2H), 3.90-3.75 (m, 1H), 3.45-3.20 (m, 5H), 3.00-2.55 (m, 5H), 2.50-2.40 (m, 1H), 1.95-1.85 (m, 1H), 0.85 (d, 3H), 0.80 (d, 3H).

#### Example 8

Cisfuran carbamate 16: To a solution of amine 14 (20.4 g, 52.0 mmol) in acetonitrile (600 mL) at room temperature was charged dimethylaminopyridine (13.4 g, 109 mmol) followed by cisfuran *p*-nitrophenylcarbonate reagent 15 (14.6 g, 49.5 mmol). The resulting solution was stirred at room temperature for at least 48 hours and monitored by TLC assay ( $\text{SiO}_2$ , 10% methanol in dichloromethane as eluent, cisfuran product  $R_f = 0.34$ , visualization by UV). The reaction mixture was concentrated via rotary evaporator. The crude product mixture was purified by silica gel column chromatography using a gradient of 60% ethyl acetate in hexanes to 70% ethyl acetate in hexanes to afford the product 16 as a solid (18.2 g, 64% yield).  $^1\text{H}$  NMR (DMSO)  $\delta$  10.4 (bs, 1H), 7.60 (d, 2H), 7.30-7.10 (m, 6H), 6.95 (d, 2H), 5.50 (d, 1H), 4.85 (m, 1H), 3.85 (m, 1H), 3.70 (m, 1H), 3.65-3.50 (m, 4H), 3.30 (d, 1H), 3.05-2.95 (m, 2H), 2.80-2.65 (m, 3H), 2.50-2.40 (m, 1H), 2.00-1.90 (m, 1H), 1.45-1.20 (m, 2H), 0.85 (d, 3H), 0.80 (d, 3H).



## Example Section L

### Example 1

Monobenzyl phosphonate 2 A solution of dibenzylphosphonate 1(150 mg, 0.175mmol) was dissolved in toluene (1 mL), treated with DABCO (20 mg, 0.178 mmol) and was refluxed under N<sub>2</sub> atmosphere (balloon) for 3 h. The solvent was removed and the residual was dissolved in aqueous HCl (5%). The aqueous layer was extracted with ethyl acetate and the organic layer was dried over sodium sulfate. After evaporation to yield the monobenzyl phosphonate 2 (107 mg, 80%) as a white powder. <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.75 (d, J = 5.4 Hz, 2H), 7.42-7.31 (m, 5H) 7.16 (d, J = 5.4 Hz, 2H), 7.01 (d, J = 5.4 Hz, 2H), 6.86 (d, J = 5.4 Hz, 2H), 5.55 (d, J = 3.3 Hz, 1H), 5.14 (d, J = 5.1 Hz, 2H), 4.91 (m, 1H), 4.24-3.66 (m overlapping s, 11H), 3.45 (m, 2H), 3.14-2.82 (m, 6H), 2.49 (m, 1H), 2.01 (m, 1H), 1.51-1.34 (m, 2H), 0.92 (d, J = 3.9 Hz, 3H), 0.87 (d, J = 3.9 Hz, 3H); <sup>31</sup>P NMR (CD<sub>3</sub>OD) δ 20.5; MS (ESI) 761 (M-H).

### Example 2

Monobenzyl, ethyl phosphonate 3 To a solution of monobenzyl phosphonate 2 (100 mg, 0.13 mmol) in dry THF (5 mL) at room temperature under N<sub>2</sub> was added Ph<sub>3</sub>P (136 mg, 0.52 mmol) and ethanol (30 μL, 0.52 mmol). After cooled to 0°C, DEAD (78μL, 0.52 mmol) was added. The mixture was stirred for 20 h at room temperature. The solvent was evaporated under reduced pressure and the residue was purified by using chromatograph on silica gel (10% to 30% ethyl acetate / hexane) to afford the monobenzyl, ethyl phosphonate 3 (66 mg, 64%) as white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.70 (d, J = 8.7 Hz, 2H), 7.43-7.34 (m, 5H) 7.14 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.7Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 5.56 (d, J = 5.4 Hz, 1H), 5.19 (d, J = 8.7 Hz, 2H), 5.00 (m, 2H), 4.22-3.67 (m overlapping s, 13H), 3.18-2.76 (m, 7H), 1.82-1.54 (m, 3H), 1.33 (t, J = 7.0 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 19.8; MS (ESI) 813 (M+Na).

### Example 3

Monoethyl phosphonate 4 A solution of monobenzyl, ethyl phosphonate 3 (60 mg) was dissolved in EtOAc (2 mL), treated with 10% Pd/C (6 mg) and was stirred under H<sub>2</sub> atmosphere (balloon) for 2h. The catalyst was removed by filtration through celite. The filtered was evaporated under reduced pressure, the residue was triturated with ether and the

solid was collected by filtration to afford the monoethyl phosphonate 4 (50 mg, 94%) as white solid.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ) 7.76 (d,  $J = 8.7$  Hz, 2H), 7.18 (d,  $J = 8.4$  Hz, 2H), 7.01 (d,  $J = 8.7$  Hz, 2H), 6.89 (d,  $J = 8.4$  Hz, 2H), 5.58 (d,  $J = 5.4$  Hz, 1H), 5.90 (m, 1H), 4.22-3.67 (m overlapping s, 13H), 3.18-2.50 (m, 7H), 1.98 (m, 1H), 1.56 (m, 2H), 1.33 (t,  $J = 6.9$  Hz, 3H), 0.92 (d,  $J = 6.6$  Hz, 3H), 0.87 (d,  $J = 6.6$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  18.7; MS (ESI) 700 (M-H).

#### Example 4

Monophenyl, ethyl phosphonate 5 To a solution of phosphonic acid 11 (800 mg, 1.19 mmol) and phenol (1.12 g, 11.9 mmol) in pyridine (8 mL) was added ethanol (69  $\mu\text{L}$ , 1.19 mmol) and 1, 3-dicyclohexylcarbodiimide (1g, 4.8 mmol). The solution was stirred at 70°C for 2h. The reaction mixture was cooled to room temperature, then diluted with ethyl acetate (10 mL) and filtered. The filtrate was evaporated under reduced pressure to remove pyridine. The residue was dissolved in ethyl acetate and the organic phase was separated and washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated. The residue was purified by chromatography on silica gel to give monophenyl, ethyl phosphonate 5 (600 mg, 65%) as white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 7.72 (d,  $J = 9$  Hz, 2H), 7.36-7.18 (m, 5H), 7.15 (d,  $J = 8.7$  Hz, 2H), 6.98 (d,  $J = 9$  Hz, 2H), 6.87 (d,  $J = 8.7$  Hz, 2H), 5.64 (d,  $J = 5.4$  Hz, 1H), 5.00 (m, 2H), 4.34 (m, 4H), 3.94-3.67 (m overlapping s, 9H), 3.18-2.77 (m, 7H), 1.82-1.54 (m, 3H), 1.36 (t,  $J = 7.2$  Hz, 3H), 0.92 (d,  $J = 6.6$  Hz, 3H), 0.87 (d,  $J = 6.6$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  16.1; MS (ESI) 799 (M+Na).

#### Example 5

Sulfonamide 6 To a suspension of epoxide 5 (3 g, 8.12 mmol) in 2-propanol (30 mL) was added isobutylamine (8 mL, 81.2 mmol) and the solution was stirred at 80°C for 1 h. The solution was evaporated under reduced pressure and the crude solid was dissolved in  $\text{CH}_2\text{Cl}_2$  (40 mL) and cooled to 0°C. TEA (2.3 mL, 16.3 mmol) was added followed by the addition of 4-nitrobenzenesulfonyl chloride (1.8 g, 8.13 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) and the solution was stirred for 30 min at 0°C, warmed to room temperature and evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated  $\text{NaHCO}_3$ . The organic phase was washed with saturated NaCl, dried over  $\text{Na}_2\text{SO}_4$ , filtered and evaporated under reduced pressure. The crude product was recrystallized from EtOAc/hexane to give the sulfonamide 6 (4.6 g, 91%) as an off-white solid. MS (ESI) 650 (M+Na).

Example 6

Phenol 7 A solution of sulfonamide 6 (4.5 g, 7.1 mmol) in  $\text{CH}_2\text{Cl}_2$  (50 mL) at  $0^\circ\text{C}$  was treated with  $\text{BBr}_3$  (1M in  $\text{CH}_2\text{Cl}_2$ , 50mL). The solution was stirred at  $0^\circ\text{C}$  to room temperature for 48h.  $\text{CH}_3\text{OH}$  (10 mL) was carefully added. The solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and saturated  $\text{NaHCO}_3$ . The organic phase washed with saturated NaCl, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (10% -  $\text{MeOH}/\text{CH}_2\text{Cl}_2$ ) to give the phenol 7 (2.5 g, 80%) as an off-white solid. MS (ESI) 528 (M+H).

Example 7

Carbamate 8 A solution of sulfonamide 7 (2.5 g, 5.7 mmol) in  $\text{CH}_3\text{CN}$  (100 mL) and was treated with proton-sponge (3 g, 14 mmol) and followed by (3R, 3aR, 6aS)-hexahydrofuro[2,3-b]furan-2-yl 4-nitrophenyl carbonate (1.7 g, 5.7 mmol) at  $0^\circ\text{C}$ . After stirring for 48h at room temperature, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 10% HCl. The organic phase was washed with saturated NaCl, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (10%  $\text{MeOH}/\text{CH}_2\text{Cl}_2$ ) affording the carbamate 8 (2.1g, 62 %) as a white solid. MS (ESI) 616 (M+Na).

Example 8

Diethylphosphonate 9 To a solution of carbamate 8 (2.1 g, 3.5 mmol) in  $\text{CH}_3\text{CN}$  (50 mL) was added  $\text{Cs}_2\text{CO}_3$  (3.2 g, 9.8 mmol) and diethyltriflate (1.6g, 5.3 mmol). The mixture was stirred at room temperature for 1h. After removed the solvent, the residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (1% to 5%  $\text{MeOH}/\text{CH}_2\text{Cl}_2$ ) to afford the diethylphosphonate 9 as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.35 (d, J = 9 Hz, 2H), 7.96 (d, J = 9 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 5.63 (d, J = 5.1 Hz, 1H), 5.18-5.01 (m, 2H), 4.27-4.17 (m, 6H), 3.94-3.67 (m, 7H), 3.20-2.73 (m, 7H), 1.92-1.51 (m, 3H), 1.35 (t, J = 7.2 Hz, 6H), 0.88-0.85 (m, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.2; MS (ESI) 756 (M+Na).

Example 9

Amine 10 A solution of diethylphosphonate 9 (1 g) was dissolved in EtOH (100 mL), treated with 10% Pd/C (300 mg) and was stirred under H<sub>2</sub> atmosphere (balloon) for 3h. The reaction was purged with N<sub>2</sub>, and the catalyst was removed by filtration through celite. After evaporation of the filtrate, the residue was triturated with ether and the solid was collected by filtration to afford the amine 10 (920 mg, 96%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.41 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 6.68 (d, J = 8.4 Hz, 2H), 5.67 (d, J = 5.1 Hz, 1H), 5.13-5.05 (m, 2H), 4.42 (s, 2H), 4.29-4.20 (m, 6H), 4.00-3.69 (m, 7H), 3.00-2.66 (m, 7H), 1.80-1.69 (m, 3H), 1.38 (m, 6H), 0.94 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 6.4 Hz, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 19.4; MS (ESI) 736 (M+Na).

10

Compound	R <sub>1</sub>	R <sub>2</sub>
16a	Gly-Et	Gly-Et
16b	Gly-Bu	Gly-Bu
16j	Phe-Bu	Phe-Bu
16k	NHEt	NHEt

#### Example 10

Synthesis of Bisamidates 16a. A solution of phosphonic acid 11 (100 mg, 0.15 mmol) L-alanine ethyl ester hydrochloride (84 mg, 0.6 mmol) was dissolved in pyridine (5 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph<sub>3</sub>P (118 mg, 0.45 mmol) and 2,2'-dipyridyl disulfide (99 mg, 0.45 mmol) in pyridine (1 mL) stirring for 20h at room temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (1% to 5% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>). The purified product was suspended in ether and was evaporated under reduced pressure to afford bisamidate 16a (90 mg, 72%) as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.72 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.68 (d, J = 5.1 Hz, 1H), 5.05 (m, 1H), 4.25 (d, J = 9.9 Hz, 2H), 4.19 (q, 4H), 3.99-3.65 (m overlapping s, 13H), 3.41 (m, 1H), 3.20-2.81 (m, 7H), 1.85-1.60 (m, 3H), 1.27 (t, J = 7.2 Hz, 6H), 0.93 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 21.8; MS (ESI) 843 (M+H).

#### Example 11

Synthesis of Bisamidates 16b. A solution of phosphonic acid 11 (100 mg, 0.15 mmol) L-alanine n-butyl ester hydrochloride (101 mg, 0.6 mmol) was dissolved in pyridine (5 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph<sub>3</sub>P (118 mg, 0.45 mmol) and 2,2'-dipyridyl disulfide (99 mg, 0.45 mmol) in pyridine (1 mL) stirring for 20h at room temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (1% to 5% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>). The purified product was suspended in ether and was evaporated under reduced pressure to afford bisamidate 16b (100 mg, 74%) as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.72 (d, J = 9 Hz, 2H), 7.15 (d, J = 9 Hz, 2H), 7.01 (d, J = 9 Hz, 2H), 6.87 (d, J = 9 Hz, 2H), 5.67 (d, J = 5.4 Hz, 1H), 5.05 (m, 1H), 4.96 (m, 1H), 4.25 (d, J = 9.9 Hz, 2H), 4.11 (t, J = 6.9 Hz, 4H), 3.99-3.71 (m overlapping s, 13H), 3.41 (m, 1H), 3.20-2.80 (m, 7H), 1.87-1.60 (m, 7H), 1.42 (m, 4H), 0.96-0.88 (m, 12H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 21.8; MS (ESI) 890 (M+H).

#### Example 12

Synthesis of Bisamidates 16j. A solution of phosphonic acid 11 (100 mg, 0.15 mmol) L-phenylalanine n-butyl ester hydrochloride (155 mg, 0.6 mmol) was dissolved in pyridine (5 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph<sub>3</sub>P (118 mg, 0.45 mmol) and 2,2'-dipyridyl disulfide (99 mg, 0.45 mmol) in pyridine (1 mL) stirring for 36h at room temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (1% to 5% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>). The purified product was suspended in ether and was evaporated under reduced pressure to afford bisamidate 16j (106 mg, 66%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.72 (d, J = 8.7 Hz, 2H), 7.31-7.10 (m, 12H), 7.01 (d, J = 9 Hz, 2H), 6.72 (d, J = 8.7 Hz, 2H), 5.67 (d, J = 5.1 Hz, 1H), 5.05 (m, 1H), 4.96 (m, 1H), 4.35-3.98 (m, 7H), 3.90-3.61 (m overlapping s, 10H), 3.19-2.78 (m, 11H), 1.87-1.25 (m, 11H), 0.96-0.88 (m, 12H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 19.3; MS (ESI) 1080 (M+H).

#### Example 13

Synthesis of Bisamidates 16k. A solution of phosphonic acid 11 (80 mg, 0.12 mmol), ethylamine (0.3 mL, 2M in THF, 0.6 mmol) was dissolved in pyridine (5 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph<sub>3</sub>P (109 mg, 0.42 mmol) and 2,2'-dipyridyl disulfide (93 mg, 0.42 mmol) in pyridine (1 mL) stirring for 48h at room temperature. The solvent was evaporated under reduced

pressure and the residue was chromatographed on silica gel (1% to 5% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>). The purified product was suspended in ether and was evaporated under reduced pressure to afford bisamidate 16k (60 mg, 70%) as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.72 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.67 (d, J = 5.1 Hz, 1H), 5.05-4.95 (m, 2H), 4.15 (d, J = 9.6 Hz, 2H), 3.99-3.72 (m overlapping s, 9H), 3.18-2.81 (m, 11H), 2.55 (br, 1H), 1.85-1.65 (m, 3H), 1.18 (t, J = 7.2 Hz, 6H), 0.93 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 21.6; MS (ESI) 749 (M+Na).

Compound	R <sub>1</sub>	R <sub>2</sub>
30a	OPh	Ala-Me
30b	OPh	Ala-Et
30c	OPh	(D)-Ala-iPr
30d	OPh	Ala-Bu
30e	OBn	Ala-Et

#### 10 Example 14

Monoamidate 30a (R<sub>1</sub> = OPh, R<sub>2</sub> = Ala-Me) To a flask was charged with monophenyl phosphonate 29 (75 mg, 0.1 mmol), L-alanine methyl ester hydrochloride (4.0 g, 22 mmol) and 1, 3-dicyclohexylcarbodiimide (84 mg, 0.6 mmol), then pyridine (1 mL) was added under N<sub>2</sub>. The resulted mixture was stirred at 60 – 70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was partitioned between ethyl acetate and HCl (0.2 N), the ethyl acetate phase was washed with water and NaHCO<sub>3</sub>, dried over Na<sub>2</sub>SO<sub>4</sub> filtered and concentrated. The residue was purified by chromatography on silica gel (ethyl acetate/hexane 1:5) to give 30a (25 mg, 30%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.24 (m, 5H) 7.19-7.15 (m, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.90-6.83 (m, 2H), 5.65 (d, J = 5.1 Hz, 1H), 5.01 (m, 2H), 4.30 (m, 2H), 3.97-3.51 (m overlapping s, 12H), 3.20-2.77 (m, 7H), 1.81 (m, 1H), 1.58 (m, 3H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 20.4 and 19.3; MS (ESI) 856 (M+Na).

#### 25 Example 15

Monoamidate 30b (R<sub>1</sub> = OPh, R<sub>2</sub> = Ala-Et) was synthesized in the same manner in 35% yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.24 (m, 5H) 7.19-7.15 (m, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.90-6.83 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.01 (m, 3H), 4.30 -3.67

(m overlapping s, 14H), 3.18-2.77 (m, 7H), 1.81-1.35 (m, 6H), 1.22 (m, 3H), 0.92 (d,  $J = 6.3$  Hz, 3H), 0.88 (d,  $J = 6.3$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.4 and 19.3; MS (ESI) 870 ( $\text{M}+\text{Na}$ ).

#### Example 16

- 5 Monoamidate 30c ( $\text{R}_1 = \text{OPh}$ ,  $\text{R}_2 = (\text{D})\text{-Ala-iPr}$ ) was synthesized in the same manner in 52% yield. Isomer A  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.72 (d,  $J = 8.7$  Hz, 2H), 7.73-7.24 (m, 5H) 7.19-7.15 (m, 2H), 7.01 (d,  $J = 8.7$  Hz, 2H), 6.90-6.83 (m, 2H), 5.66 (m, 1H), 5.01 (m, 3H), 4.30-3.67 (m overlapping s, 14H), 3.18-2.77 (m, 7H), 1.81-1.35 (m, 6H), 1.23 (m, 6H), 0.92 (d,  $J = 6.3$  Hz, 3H), 0.88 (d,  $J = 6.3$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.4; MS (ESI) 884 ( $\text{M}+\text{Na}$ ). Isomer
- 10 B  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.72 (d,  $J = 8.7$  Hz, 2H), 7.73-7.24 (m, 5H) 7.19-7.15 (m, 2H), 7.01 (d,  $J = 8.7$  Hz, 2H), 6.90-6.83 (m, 2H), 5.66 (m, 1H), 5.01 (m, 3H), 4.30-3.67 (m overlapping s, 14H), 3.18-2.77 (m, 7H), 1.81-1.35 (m, 6H), 1.23 (m, 6H), 0.92 (d,  $J = 6.3$  Hz, 3H), 0.88 (d,  $J = 6.3$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.3; MS (ESI) 884 ( $\text{M}+\text{Na}$ ).

#### 15 Example 17

- Monoamidate 30d ( $\text{R}_1 = \text{OPh}$ ,  $\text{R}_2 = \text{Ala-Bu}$ ) was synthesized in the same manner in 25% yield.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.72 (d,  $J = 8.7$  Hz, 2H), 7.73-7.24 (m, 5H) 7.19-7.15 (m, 2H), 7.01 (d,  $J = 8.7$  Hz, 2H), 6.90-6.83 (m, 2H), 5.65 (d,  $J = 5.4$  Hz, 1H), 5.01 (m, 3H), 4.30-3.67 (m overlapping s, 16H), 3.18-2.77 (m, 7H), 1.81-1.35 (m, 8H), 1.22 (m, 3H), 0.92 (d,  $J = 6.3$  Hz, 3H), 0.88 (d,  $J = 6.3$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.4 and 19.4; MS (ESI) 898 ( $\text{M}+\text{Na}$ ).
- 20

#### Example 18

- Monoamidate 30e ( $\text{R}_1 = \text{OBn}$ ,  $\text{R}_2 = \text{Ala-Et}$ ) To a flask was charged with monobenzyl
- 25 phosphonate 2 (76 mg, 0.1 mmol), L-alanine methyl ester hydrochloride (4.0 g, 22 mmol) and 1, 3-dicyclohexylcarbodiimide (84 mg, 0.6 mmol), then pyridine (1 mL) was added under  $\text{N}_2$ . The resulted mixture was stirred at 60 – 70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was partitioned between ethyl acetate and HCl (0.2 N), the ethyl acetate phase was
- 30 washed with water and  $\text{NaHCO}_3$ , dried over  $\text{Na}_2\text{SO}_4$  filtered and concentrated. The residue was purified by chromatography on silica gel (ethyl acetate / hexane 1:5) to give 30a (25 mg, 30%) as a white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.72 (d,  $J = 8.7$  Hz, 2H), 7.38-7.34 (m, 5H), 7.13

(d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.86-6.80 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.15-5.01 (m, 5H), 4.30-3.67 (m overlapping s, 14H), 3.18-2.77 (m, 7H), 1.81-1.35 (m, 6H), 1.22 (m, 3H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  23.3 and 22.4; MS (ESI) 884 (M+Na).

5

Compound	R <sub>1</sub>	R <sub>2</sub>
31a	OPh	Lac-iPr
31b	OPh	Lac-Et
31c	OPh	Lac-Bu
31d	OPh	(R)-Lac-Me
31e	OPh	(R)-Lac-Et

### Example 19

Monolactate 31a (R<sub>1</sub> = OPh, R<sub>2</sub> = Lac-iPr): To a flask was charged with monophenyl phosphonate 29 (1.5 g, 2 mmol), isopropyl-(s)-lactate (0.88 mL, 6.6 mmol) and 1, 3-  
 10 dicyclohexylcarbodiimide (1.36 g, 6.6 mmol), then pyridine (15 mL) was added under N<sub>2</sub>. The resulted mixture was stirred at 60 – 70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was washed with ethyl acetate and the combined organic phase was washed with NH<sub>4</sub>Cl, brine and water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was  
 15 purified by chromatography on silica gel (ethyl acetate / CH<sub>2</sub>Cl<sub>2</sub> 1:5) to give 31a (1.39g, 81%) as a white solid. Isomer A  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.72 (d, J = 8.7 Hz, 2H), 7.73-7.19 (m, 5H), 7.15 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.15-5.00 (m, 4H), 4.56-4.44 (m, 2H), 3.96-3.68 (m overlapping s, 9H), 3.13-2.78 (m, 7H), 1.81-1.23 (m, 6H), 1.22 (m, 6H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz,  
 20 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.4; MS (ESI) 885 (M+Na). Isomer B  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.72 (d, J = 8.7 Hz, 2H), 7.73-7.19 (m, 5H), 7.14 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 5.64 (d, J = 5.4 Hz, 1H), 5.15-5.00 (m, 4H), 4.53-4.41 (m, 2H), 3.96-3.68 (m overlapping s, 9H), 3.13-2.78 (m, 7H), 1.81-1.23 (m, 6H), 1.22 (m, 6H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  15.3; MS (ESI) 885 (M+Na).

25

### Example 20

Monolactate 31b (R<sub>1</sub> = OPh, R<sub>2</sub> = Lac-Et) was synthesized in the same manner in 75% yield.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.72 (d, J = 8.7 Hz, 2H), 7.73-7.14 (m, 7H), 6.99 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.63 (m, 1H), 5.19-4.95 (m, 3H), 4.44-4.40 (m, 2H), 4.17-4.12 (m,



2H), 3.95-3.67 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.58 (m, 6H), 1.23 (m, 3H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.5 and 15.4; MS (ESI) 872 (M+Na).

5 Example 21

Monolactate 31c (R1 = OPh, R2 = Lac-Bu) was synthesized in the same manner in 58% yield. Isomer A  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.72 (d, J = 8.7 Hz, 2H), 7.73-7.19 (m, 5H), 7.14 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 5.63 (d, J = 5.4 Hz, 1H), 5.15-5.00 (m, 3H), 4.56-4.51 (m, 2H), 4.17-4.10 (m, 2H), 3.95-3.67 (m overlapping s, 9H), 3.10-2.77 (m, 7H), 1.81-1.23 (m, 10H), 1.23 (m, 6H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.3; MS (ESI) 899 (M+Na). Isomer B  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.72 (d, J = 8.7 Hz, 2H), 7.73-7.19 (m, 5H), 7.14 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 5.64 (d, J = 5.4 Hz, 1H), 5.15-5.00 (m, 3H), 4.44-4.39 (m, 2H), 4.17-4.10 (m, 2H), 3.95-3.67 (m overlapping s, 9H), 3.10-2.77 (m, 7H), 1.81-1.23 (m, 10H), 1.23 (m, 6H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  15.3; MS (ESI) 899 (M+Na).

Example 22

Monolactate 31d (R1 = OPh, R2 = (R)-Lac-Me): To a stirred solution of monophenyl phosphonate 29 (100 mg, 0.13 mmol) in 10 mL of THF at room temperature under  $\text{N}_2$  was added methyl-(S)-lactate (54 mg, 0.52 mmol) and  $\text{Ph}_3\text{P}$  (136 mg, 0.52 mmol), followed by DEAD (82  $\mu\text{L}$ , 0.52 mmol). After 2 h, the solvent was removed under reduced pressure, and the resulting crude mixture was purified by chromatography on silica gel (ethyl acetate / hexane 1:1) to give 31d (33 mg, 30%) as a white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.72 (d, J = 8.7 Hz, 2H), 7.73-7.14 (m, 7H), 6.99 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.63 (m, 1H), 5.19-4.95 (m, 3H), 4.44-4.40 (m, 2H), 3.95-3.64 (m overlapping s, 12H), 3.15-2.77 (m, 7H), 1.81-1.55 (m, 4H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.4 and 15.3; MS (ESI) 857 (M+Na).

30 Example 23

Monolactate 31e (R1 = OPh, R2 = (R)-Lac-Et): To a stirred solution of monophenyl phosphonate 29 (50 mg, 0.065 mmol) in 2.5 mL of THF at room temperature under  $\text{N}_2$  was

added ethyl-(s)-lactate (31 mg, 0.52 mmol) and  $\text{Ph}_3\text{P}$  (68 mg, 0.26 mmol), followed by DEAD (41  $\mu\text{L}$ , 0.52 mmol). After 2 h, the solvent was removed under reduced pressure, and the resulting crude mixture was purified by chromatography on silica gel (ethyl acetate / hexane 1:1) to give 31e (28 mg, 50%) as a white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.72 (d,  $J$  = 8.7 Hz, 2H), 7.73-7.14 (m, 7H), 6.99 (d,  $J$  = 8.7 Hz, 2H), 6.85 (m, 2H), 5.63 (m, 1H), 5.19-4.95 (m, 3H), 4.44-4.40 (m, 2H), 4.17-4.12 (m, 2H), 3.95-3.67 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.58 (m, 6H), 1.23 (m, 3H), 0.91 (d,  $J$  = 6.6 Hz, 3H), 0.87 (d,  $J$  = 6.6 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.5 and 15.4; MS (ESI) 872 ( $\text{M}+\text{Na}$ ).

#### 10 Example 24

Monolactate 32 ( $\text{R}_1 = \text{OBn}$ ,  $\text{R}_2 = (\text{S})\text{-Lac-Bn}$ ): To a stirred solution of monobenzyl phosphonate 2 (76 mg, 0.1 mmol) in 0.5 mL of DMF at room temperature under  $\text{N}_2$  was added benzyl-(s)-lactate (27 mg, 0.15 mmol) and PyBOP (78 mg, 0.15 mmol), followed by DIEA (70  $\mu\text{L}$ , 0.4 mmol). After 3 h, the solvent was removed under reduced pressure, and the resulting crude mixture was purified by chromatography on silica gel (ethyl acetate / hexane 1:1) to give 32 (46 mg, 50%) as a white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.72 (d,  $J$  = 8.7 Hz, 2H), 7.38-7.44 (m, 10H), 7.13 (d,  $J$  = 8.4 Hz, 2H), 6.99 (d,  $J$  = 8.7 Hz, 2H), 6.81 (m, 2H), 5.63 (d,  $J$  = 5.1 Hz, 1H), 5.23-4.92 (m, 7H), 4.44-2.22 (m, 2H), 3.96-3.67 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.58 (m, 6H), 0.93 (d,  $J$  = 6.3 Hz, 3H), 0.88 (d,  $J$  = 6.3 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.8 and 19.6; MS (ESI) 947 ( $\text{M}+\text{Na}$ ).

#### Example 25

Monolactate 33 ( $\text{R}_1 = \text{OBn}$ ,  $\text{R}_2 = (\text{R})\text{-Lac-Bn}$ ): To a stirred solution of monobenzyl phosphonate 2 (76 mg, 0.1 mmol) in 5 mL of THF at room temperature under  $\text{N}_2$  was added benzyl-(s)-lactate (72 mg, 0.4 mmol) and  $\text{Ph}_3\text{P}$  (105 mg, 0.4 mmol), followed by DEAD (60  $\mu\text{L}$ , 0.4 mmol). After 20 h, the solvent was removed under reduced pressure, and the resulting crude mixture was purified by chromatography on silica gel (ethyl acetate / hexane 1:1) to give 33 (44 mg, 45%) as a white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.72 (d,  $J$  = 8.7 Hz, 2H), 7.38-7.44 (m, 10H), 7.13 (m, 2H), 6.99 (d,  $J$  = 8.7 Hz, 2H), 6.81 (m, 2H), 5.63 (m, 1H), 5.23-4.92 (m, 7H), 4.44-2.22 (m, 2H), 3.96-3.67 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.58 (m, 6H), 0.93 (d,  $J$  = 6.3 Hz, 3H), 0.88 (d,  $J$  = 6.3 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.8 and 19.6; MS (ESI) 947 ( $\text{M}+\text{Na}$ ).

Example 26

Monophosphonic acid 34: A solution of monobenzyllactate 32 (20 mg) was dissolved in EtOH/ EtOAc (3 mL/1 mL), treated with 10% Pd/C (4 mg) and was stirred under H<sub>2</sub> atmosphere (balloon) for 1.5 h. The catalyst was removed by filtration through celite. The filtered was evaporated under reduced pressure, the residue was triturated with ether and the solid was collected by filtration to afford the monophosphonic acid 33 (15 mg, 94%) as a white solid. <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.76 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 5.69 (d, J = 5.7 Hz, 1H), 5.03-4.95 (m, 2H), 4.20 (m, 2H), 3.90-3.65 (m overlapping s, 9H), 3.41 (m, 2H), 3.18-2.78 (m, 5H), 2.44 (m, 1H), 2.00 (m, 1H), 1.61-1.38 (m, 5H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); <sup>31</sup>P NMR (CD<sub>3</sub>OD) δ 18.0; MS (ESI) 767 (M+Na).

Example 27

Monophosphonic acid 35: A solution of monobenzyllactate 33(20 mg) was dissolved in EtOH (3 mL), treated with 10% Pd/C (4 mg) and was stirred under H<sub>2</sub> atmosphere (balloon) for 1h. The catalyst was removed by filtration through celite. The filtered was evaporated under reduced pressure, the residue was triturated with ether and the solid was collected by filtration to afford the monophosphonic acid 35 (15 mg, 94%) as a white solid. <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.76 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 5.69 (d, J = 5.7 Hz, 1H), 5.03-4.95 (m, 2H), 4.20 (m, 2H), 3.90-3.65 (m overlapping s, 9H), 3.41 (m, 2H), 3.18-2.78 (m, 5H), 2.44 (m, 1H), 2.00 (m, 1H), 1.61-1.38 (m, 5H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); <sup>31</sup>P NMR (CD<sub>3</sub>OD) δ 18.0; MS (ESI) 767 (M+Na).

Example 28

Synthesis of Bis lactate 36: A solution of phosphonic acid 11 (100 mg, 0.15 mmol) isopropyl-(S)-lactate (79 mg, 0.66 mmol) was dissolved in pyridine (1 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph<sub>3</sub>P (137 mg, 0.53 mmol) and 2,2'-dipyridyl disulfide (116 mg, 0.53 mmol) in pyridine (1 mL) stirring for 20h at room temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (1% to 5% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>). The purified product was suspended in ether and was evaporated under reduced pressure to afford

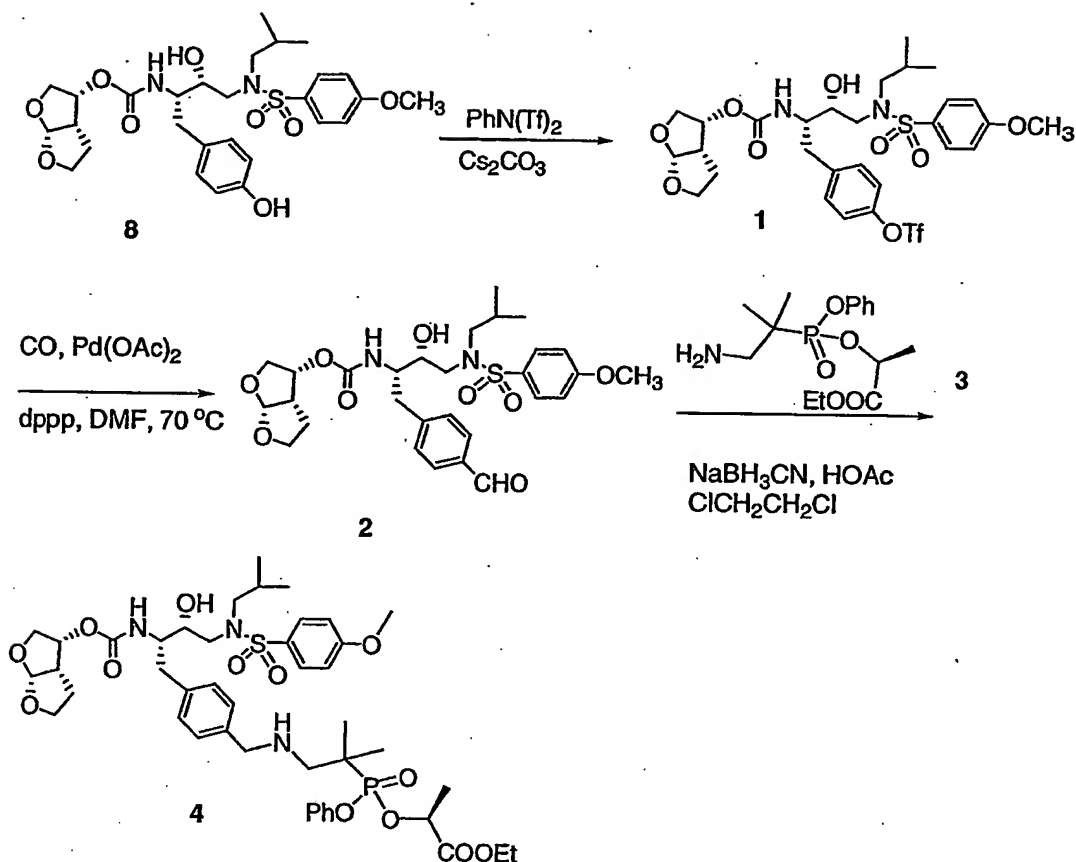
bislactate 36 (42 mg, 32%) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.72 (d,  $J$  = 8.7 Hz, 2H), 7.14 (d,  $J$  = 8.7 Hz, 2H), 7.01 (d,  $J$  = 8.7 Hz, 2H), 6.89 (d,  $J$  = 8.7 Hz, 2H), 5.66 (d,  $J$  = 5.1 Hz, 1H), 5.05 (m, 3H), 4.25 (d,  $J$  = 9.9 Hz, 2H), 4.19 (q, 4H), 3.99-3.65 (m overlapping s, 9H), 3.41 (m, 1H), 3.20-2.81 (m, 7H), 1.85-1.60 (m, 3H), 1.58 (m, 6H), 1.26 (m, 12H), 0.93 (d,  $J$  = 6.3 Hz, 3H), 0.89 (d,  $J$  = 6.3 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  21.1; MS (ESI) 923 (M+Na).

#### Example 29

Triflate derivative 1: A THF- $\text{CH}_2\text{Cl}_2$  solution (30mL-10 mL) of 8 (4 g, 6.9 mmol), cesium carbonate (2.7 g, 8 mmol), and N-phenyltrifluoromethane sulfonimide (2.8 g, 8 mmol) was reacted overnight. The reaction mixture was worked up, and concentrated to dryness to give crude triflate derivative 1.

Aldehyde 2: Crude triflate 1 (4.5 g, 6.9 mmole) was dissolved in DMF (20 mL), and the solution was degassed (high vacuum for 2 min, Ar purge, repeat 3 times).  $\text{Pd}(\text{OAc})_2$  (0.12 g, 0.27 mmol), and bis(diphenylphosphino)propane (dppp, 0.22 g, 0.27 mmol) were added and the solution was heated to 70°C. Carbon monoxide was rapidly bubbled through the solution, then under 1 atmosphere of carbon monoxide. To this solution were slowly added TEA (5.4 mL, 38 mmol), and triethylsilane (3 mL, 18 mmol). The resulting solution was stirred overnight at room temperature. The reaction mixture was worked up, and purified on silica gel column chromatograph to afford aldehyde 2 (2.1 g, 51%). (Hostetler, et al. J. Org. Chem., 1999. 64, 178-185).

Lactate prodrug 4: Compound 4 is prepared as described above procedure for 3a-e by the reductive amination between 2 and 3 with  $\text{NaBH}_3\text{CN}$  in 1,2-dichloroethane in the presence of HOAc.



### Example 30

Preparation of compound 3 Diethyl (cyano(dimethyl)methyl) phosphonate 5: A THF solution (30 mL) of NaH (3.4 g of 60% oil dispersion, 85 mmole) was cooled to  $-10^{\circ}\text{C}$ , followed by the addition of diethyl (cyanomethyl)phosphonate (5g, 28.2 mmol) and iodomethane (17 g, 112 mmol). The resulting solution was stirred at  $-10^{\circ}\text{C}$  for 2 hr, then  $0^{\circ}\text{C}$  for 1 hr, was worked up, and purified to give dimethyl derivative 5 (5 g, 86%).

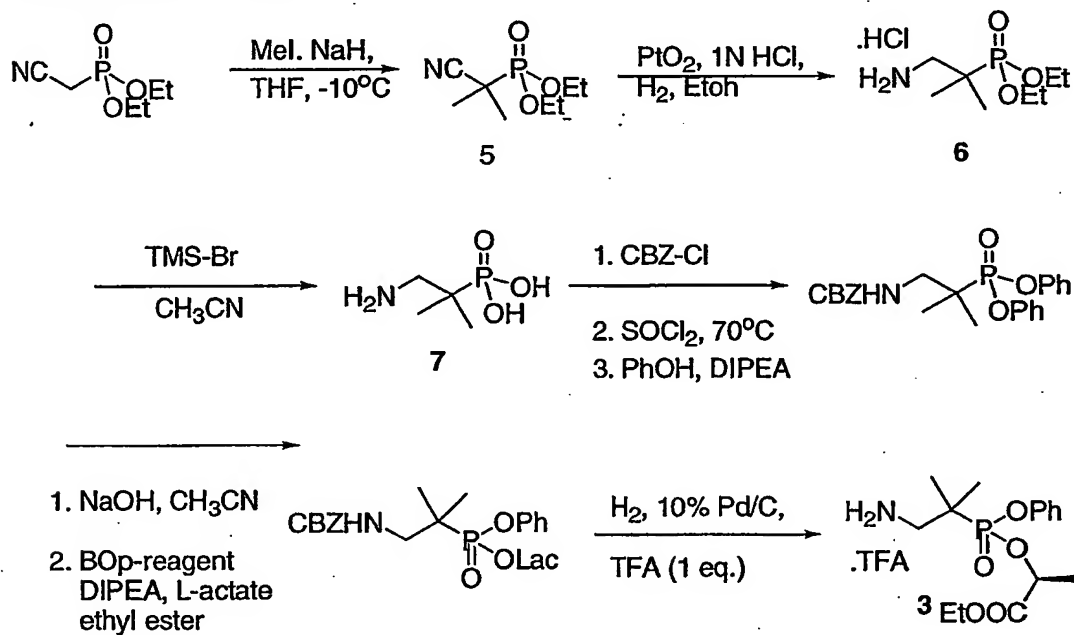
Diethyl (2-amino-1,1-diemthyl-ethyl)phosphonate 6: Compound 5 was reduced to amine derivative 6 by the described procedure (J. Med. Chem. 1999, 42, 5010-5019).

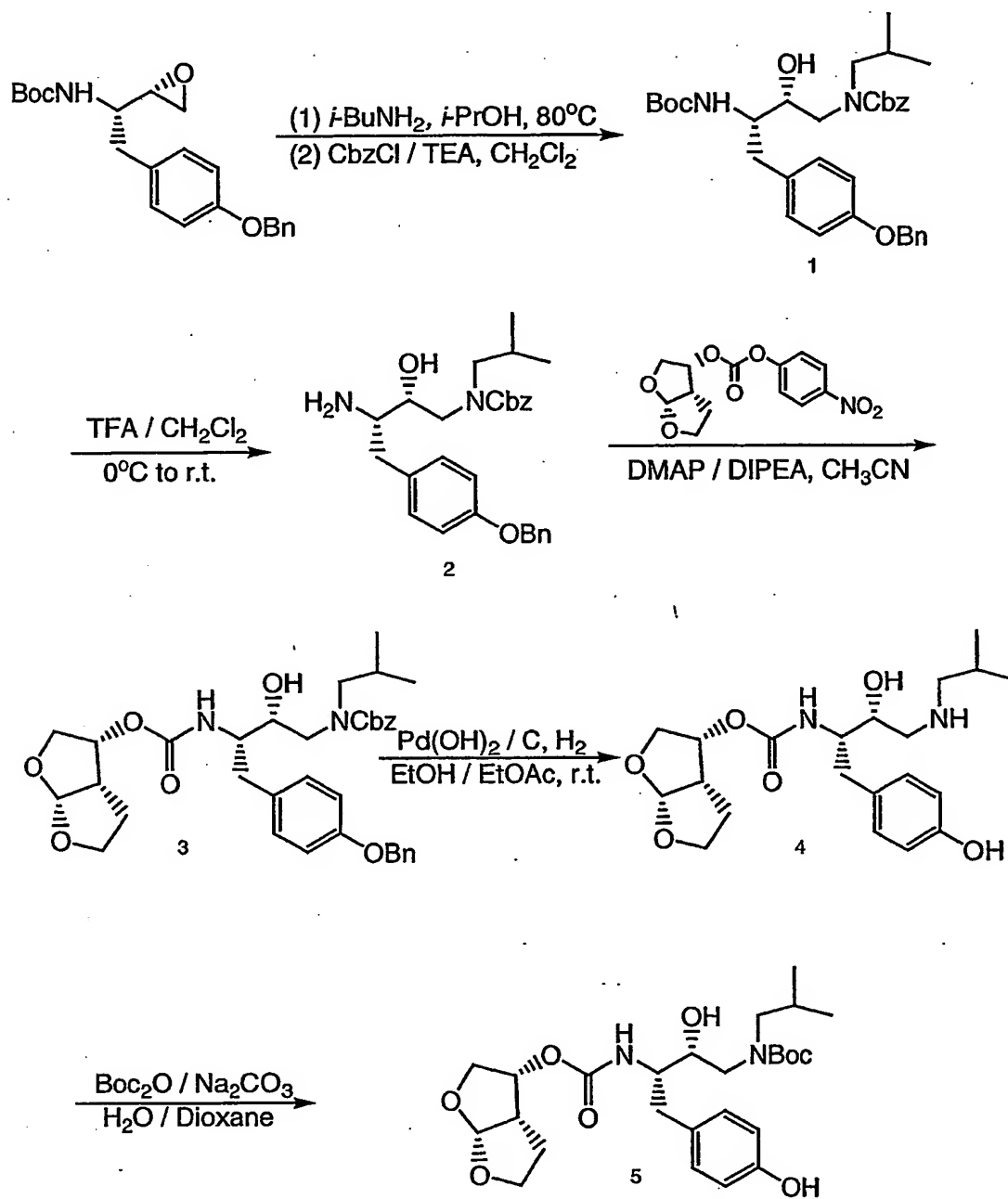
A ethanol (150 mL) and 1N HCl aqueous solution (22 mL) of 5 (2.2 g, 10.7 mmol) was hydrogenated at 1 atmosphere in the presence of PtO<sub>2</sub> (1.25 g) at room temperature overnight. The catalyst was filtered through a celite pad. The filtrate was concentrated to dryness, to give crude 6 (2.5g, as HCl salt).

2-Amino-1,1-dimethyl-ethyl phosphonic acid 7: A CH<sub>3</sub>CN (30 mL) of crude 6 (2.5 g) was cooled to  $0^{\circ}\text{C}$ , and treated with TMSBr (8 g, 52 mmol) for 5 hr. The reaction mixture was

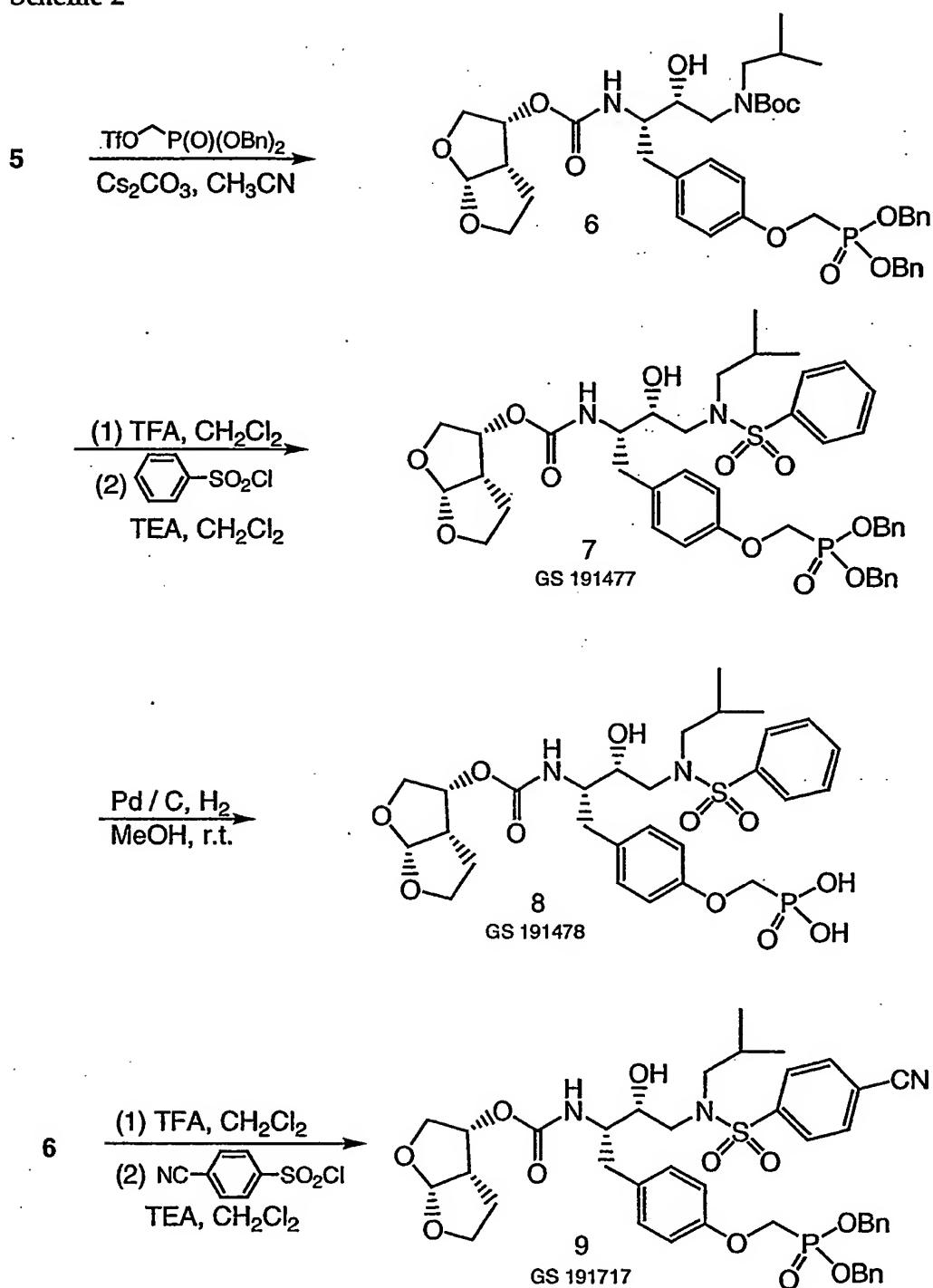
stirred with methanol for 1.5 hr at room temperature, concentrated, recharged with methanol, concentrated to dryness to give crude **7** which was used for next reaction without further purification.

- 5 Lactate phenyl (2-amino-1,1-dimethyl-ethyl)phosphonate **3**: Compound **3** is synthesized according to the procedures described in a previous scheme for the preparation of a lactate phenyl 2-aminoethyl phosphonate. Compound **7** is protected with CBZ, followed by the reaction with thionyl chloride at 70°C. The CBZ protected dichlorodate is reacted phenol in the presence of DIPEA. Removal of one phenol, follow by coupling with ethyl L-lactate leads N-CBZ-2-amino-1,1-dimethyl-ethyl phosphonated derivative. Hydrogenation of N-CBZ derivative at 1 atmosphere in the presence of 10% Pd/C and 1 equivalent of TFA affords compound **3** as TFA salt.



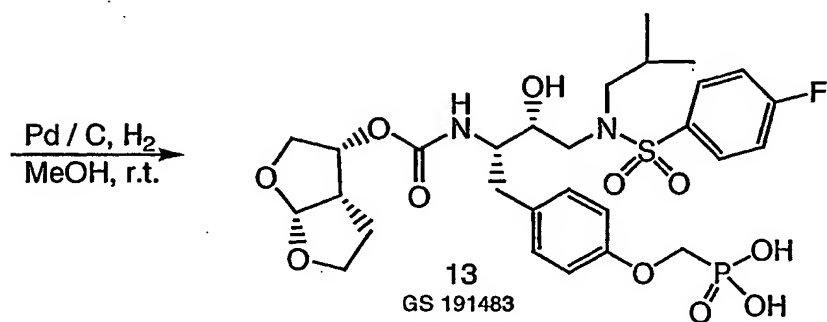
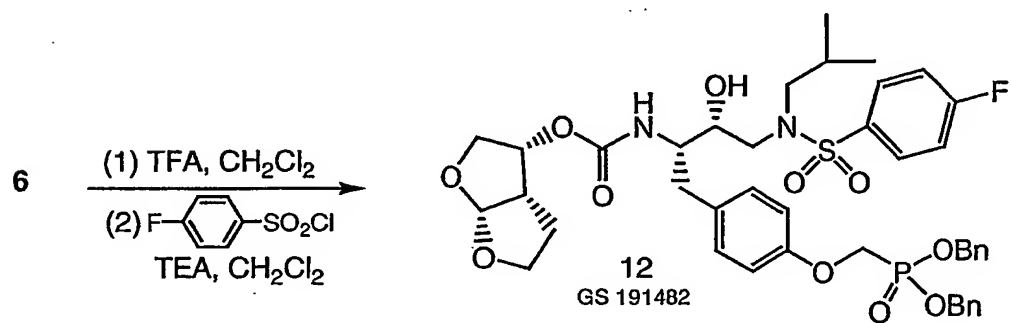
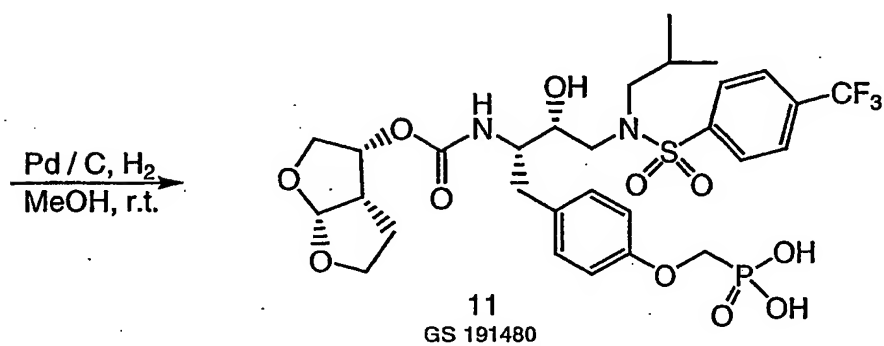
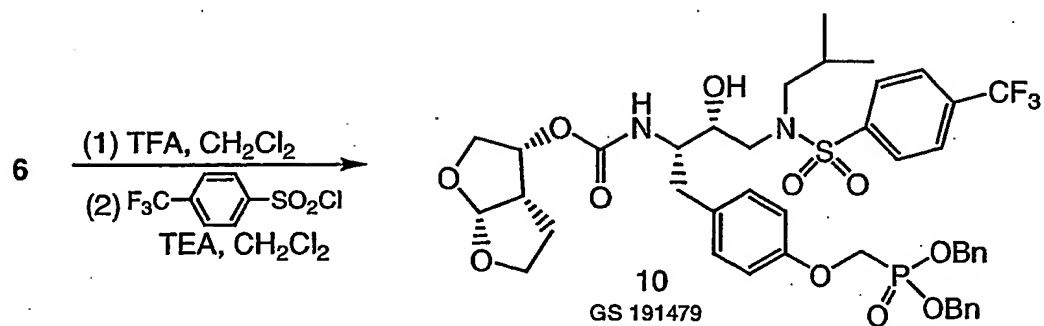
**Example Section M****Scheme 1**

Scheme 2

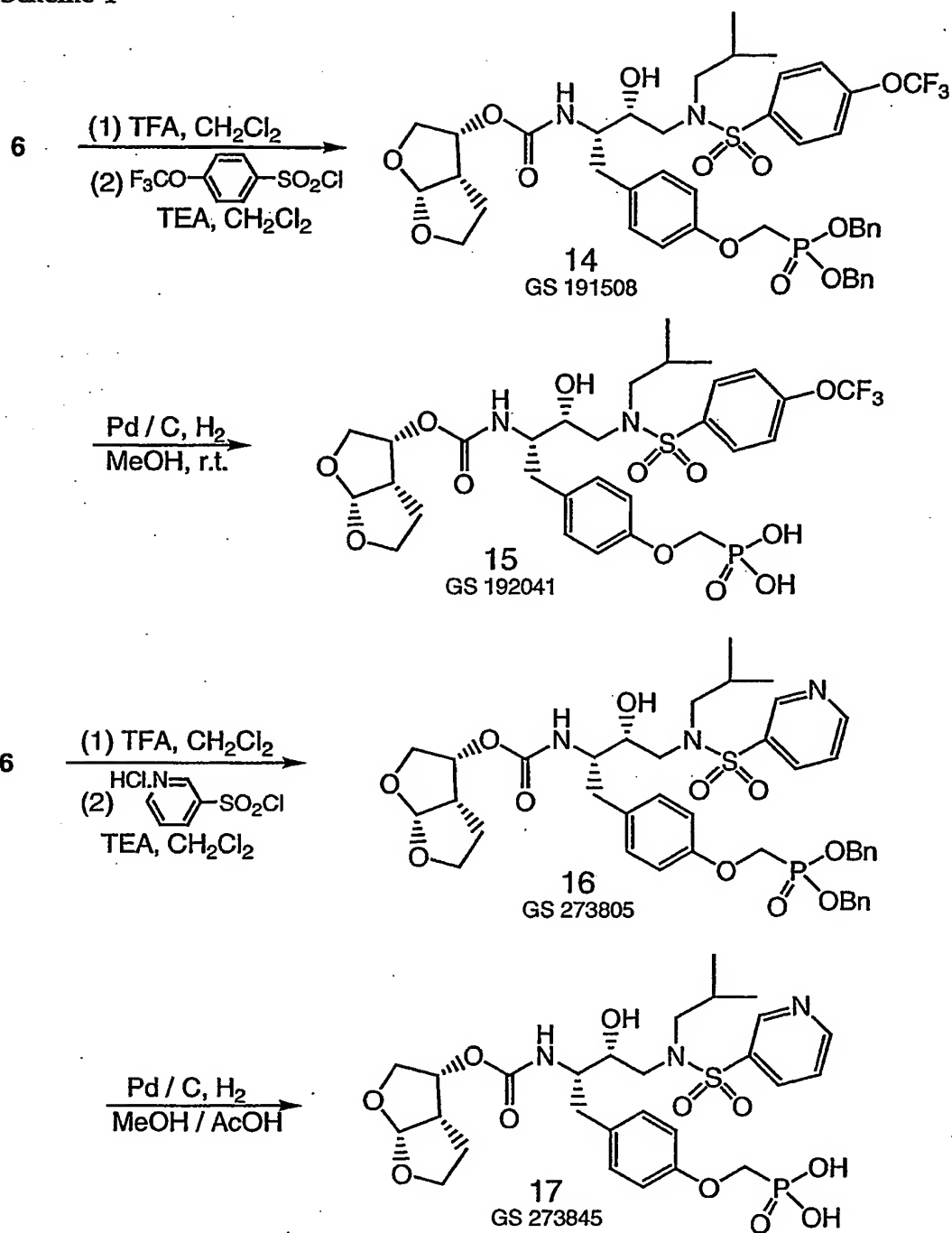




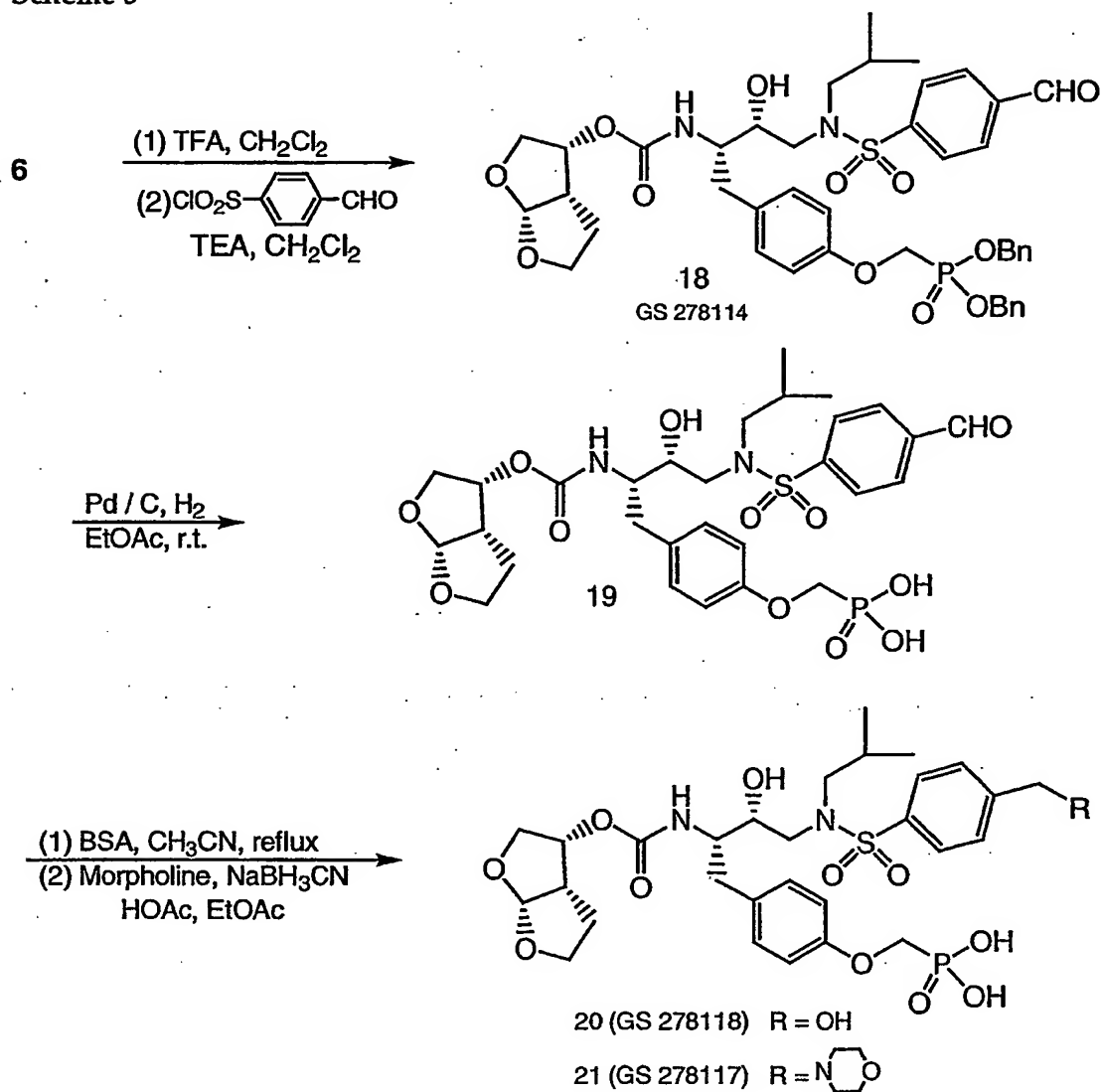
## Scheme 3



Scheme 4



## Scheme 5

Example 1

- 5    Cbz Amide 1: To a suspension of epoxide (34 g, 92.03 mmol) in 2-propanol (300 mL) was added isobutylamine (91.5 mL, 920 mmol) and the solution was refluxed for 1 h. The solution was evaporated under reduced pressure and the crude solid was dried under vacuum to give the amine (38.7 g, 95%) which was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (300 mL) and cooled to 0°C. Triethylamine (18.3 mL, 131 mmol) was added followed by the addition of benzyl
- 10    chloroformate (13.7 mL, 96.14 mmol) and the solution was stirred for 30 min at 0°C, warmed to room temperature overnight, and evaporated under reduced pressure. The residue was partitioned between EtOAc and 0.5 M H<sub>3</sub>PO<sub>4</sub>. The organic phase was washed with saturated NaHCO<sub>3</sub>, brine, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The

crude product was purified by column chromatography on silica gel (1/2-EtOAc/hexane) to give the Cbz amide (45.37 g, 90%) as a white solid.

#### Example 2

- 5 Amine 2: A solution of Cbz amide 1 (45.37 g, 78.67 mmol) in  $\text{CH}_2\text{Cl}_2$  (160 mL) at  $0^\circ\text{C}$  was treated with trifluoroacetic acid (80 mL). The solution was stirred for 30 min at  $0^\circ\text{C}$  and then warmed to room temperature for an additional 30 min. Volatiles were evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5 N NaOH (2 x), water (2 x), saturated NaCl, dried with
- 10  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure to give the amine (35.62 g, 95%) as a white solid.

#### Example 3

- Carbamate 3: To a solution of amine 2 (20.99 g, 44.03 mmol) in  $\text{CH}_3\text{CN}$  (250 mL) at  $0^\circ\text{C}$
- 15 was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (13.00 g, 44.03 mmol, prepared according to Ghosh et al. J. Med. Chem. 1996, 39, 3278.), *N,N*-diisopropylethylamine (15.50 mL, 88.06 mmol) and 4-dimethylaminopyridine (1.08 g, 8.81 mmol). The reaction mixture was stirred at  $0^\circ\text{C}$  for 30 min and then warmed to room temperature overnight. The reaction solvent was evaporated under reduced pressure and the
- 20 residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5 N NaOH (2 x), 5% citric acid (2 x), saturated  $\text{NaHCO}_3$ , dried with  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the carbamate (23.00 g, 83%) as a white solid.

25

#### Example 4

- Amine 4: To a solution of 3 (23.00 g, 36.35 mmol) in EtOH (200 mL) and EtOAc (50 mL) was added 20%  $\text{Pd}(\text{OH})_2/\text{C}$  (2.30 g). The suspension was stirred under  $\text{H}_2$  atmosphere (balloon) at room temperature for 3 h. The reaction mixture was filtered through a plug of
- 30 celite. The filtrate was concentrated and dried under vacuum to give the amine (14.00 g, 94%) as a white solid.

#### Example 5

Phenol 5: To a solution of amine 4 (14.00 g, 34.27 mmol) in H<sub>2</sub>O (80 mL) and 1,4-dioxane (80 mL) at 0°C was added Na<sub>2</sub>CO<sub>3</sub> (5.09 g, 47.98 mmol) and di-*tert*-butyl dicarbonate (8.98 g, 41.13 mmol). The reaction mixture was stirred at 0°C for 2 h and then warmed to room temperature for 30 min. The residue was partitioned between EtOAc and H<sub>2</sub>O. The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give the phenol (15.69 g, 90%) as a white solid.

#### Example 6

Dibenzylphosphonate 6: To a solution of phenol 5 (15.68 g, 30.83 mmol) in CH<sub>3</sub>CN (200 mL) was added Cs<sub>2</sub>CO<sub>3</sub> (15.07 g, 46.24 mmol) and triflate (17.00 g, 40.08 mmol). The reaction mixture was stirred at room temperature for 1 h, the salt was filtered off, and the solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the dibenzylphosphonate (15.37 g, 73%) as a white solid.

#### Example 7

Sulfonamide 7: A solution of dibenzylphosphonate 6 (0.21 g, 0.26 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL) at 0°C was treated with trifluoroacetic acid (0.25 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) and cooled to 0°C. Triethylamine (0.15 mL, 1.04 mmol) was added followed by the treatment of benzenesulfonyl chloride (47 mg, 0.26 mmol). The solution was stirred for 1 h at 0°C and the product was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and saturated NaHCO<sub>3</sub>. The organic phase was washed with saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the sulfonamide 7 (0.12 g, 55%, GS 191477) as a white solid:  
<sup>1</sup>HNMR (CDCl<sub>3</sub>) δ 7.79 (dd, 2H), 7.61-7.56 (m, 3H), 7.38-7.36 (m, 10H), 7.13 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.4 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.18 (m, 4H), 5.05 (m, 1H), 4.93 (d, J = 8.7 Hz, 1H), 4.20 (d, J = 10.2 Hz, 2H), 4.0-3.67 (m, 7H), 3.15-2.8 (m, 7H), 1.84 (m, 1H),

1.65-1.59 (m, 2H), 0.93 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.36.

#### Example 8

5 Phosphonic Acid 8: To a solution of 7 (70 mg, 0.09 mmol) in MeOH (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under  $\text{H}_2$  atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (49 mg, 90% GS 191478) as a white solid:  $^1\text{H}$ NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.83 (dd, 2H), 7.65-7.56 (m, 3H), 7.18 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 7.8 Hz, 2H), 5.59 (d, J = 5.4 Hz, 1H), 4.96 (m, 1H), 4.15 (d, J = 9.9 Hz, 2H), 3.95-3.68 (m, 6H), 3.44 (dd, 2H), 3.16 (m, 2H), 2.99-2.84 (m, 4H), 2.48 (m, 1H), 2.02 (m, 1H), 1.6 (m, 1H), 1.37 (m, 1H), 0.93 (d, J = 6.3 Hz, 3H), 0.87 (d, J = 6.3 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  17.45.

#### 15 Example 9

Sulfonamide 9: A solution of dibenzylphosphonate 6 (0.24 g, 0.31 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.5 mL) at  $0^\circ\text{C}$  was treated with trifluoroacetic acid (0.25 mL). The solution was stirred for 30 min at  $0^\circ\text{C}$  and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was  
20 co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in  $\text{CH}_2\text{Cl}_2$  (3 mL) and cooled to  $0^\circ\text{C}$ . Triethylamine (0.17 mL, 1.20 mmol) was added followed by the treatment of 4-cyanobenzenesulfonyl chloride (61.4 mg, 0.30 mmol). The solution was stirred for 1 h at  $0^\circ\text{C}$  and the product was partitioned between  $\text{CH}_2\text{Cl}_2$  and saturated  $\text{NaHCO}_3$ . The organic phase  
25 was washed with saturated NaCl, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the sulfonamide 9 (0.20 g, 77%, GS 191717) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.90 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 7.8 Hz, 2H), 7.36 (m, 10H), 7.11 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.2-4.9 (m, 5H), 4.8 (d, 1H),  
30 4.2 (d, J = 9.9 Hz, 2H), 3.99 (m, 1H), 3.94 (m, 3H), 3.7 (m, 2H), 3.48 (broad, s, 1H), 3.18-2.78 (m, 7H), 1.87 (m, 1H), 1.66-1.47 (m, 2H), 0.91 (d, J = 6.3 Hz, 3H), 0.87 (d, J = 6.3 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.3..

Example 10

Sulfonamide 10: A solution of dibenzylphosphonate 6 (0.23 g, 0.29 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.5 mL) at  $0^\circ\text{C}$  was treated with trifluoroacetic acid (0.25 mL). The solution was stirred for 30 min at  $0^\circ\text{C}$  and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in  $\text{CH}_2\text{Cl}_2$  (3 mL) and cooled to  $0^\circ\text{C}$ .

Triethylamine (0.16 mL, 1.17 mmol) was added followed by the treatment of 4-

10 trifluoromethyl benzenesulfonyl chloride (72 mg, 0.29 mmol). The solution was stirred for 1 h at  $0^\circ\text{C}$  and the product was partitioned between  $\text{CH}_2\text{Cl}_2$  and saturated  $\text{NaHCO}_3$ . The organic phase was washed with saturated  $\text{NaCl}$ , dried with  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the sulfonamide (0.13 g, 50%, GS 191479) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.92 (d,  $J$  = 8.1 Hz, 2H), 7.81 (d,  $J$  = 8.1 Hz, 2H), 7.36 (m, 10H), 7.12 (d,  $J$  = 8.4 Hz, 2H), 6.81 (d,  $J$  = 8.4 Hz, 2H), 5.65 (d,  $J$  = 5.1 Hz, 1H), 5.20-4.89 (m, 6H), 4.20 (d,  $J$  = 9.9 Hz, 2H), 3.95 (m, 1H), 3.86 (m, 3H), 3.71 (m, 2H), 3.19-2.78 (m, 7H), 1.86 (m, 1H), 1.65 (m, 2H), 0.93 (d,  $J$  = 6.3 Hz, 3H), 0.88 (d,  $J$  = 6.3 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.3.

Example 11

Phosphonic Acid 11: To a solution of 10 (70 mg, 0.079 mmol) in MeOH (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under  $\text{H}_2$  atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The

25 filtrate was concentrated and dried under vacuum to give the phosphonic acid (50 mg, 90%, GS 191480) as a white solid:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  8.03 (dd, 2H), 7.90 (dd, 2H), 7.17 (d,  $J$  = 8.1 Hz, 2H), 6.91 (d,  $J$  = 7.8 Hz, 2H), 5.59 (d,  $J$  = 5.7 Hz, 1H), 4.94 (m, 1H), 4.15 (d,  $J$  = 10.2 Hz, 2H), 3.94-3.72 (m, 6H), 3.48 (m, 1H), 3.2-3.1 (m, 3H), 3.0-2.9 (m, 2H), 2.47 (m, 1H), 2.06 (m, 1H), 1.56 (m, 1H), 1.37 (m, 1H), 0.93 (d,  $J$  = 6.3 Hz, 3H), 0.88 (d,  $J$  = 6.3 Hz, 3H);  
30  $^{31}\text{P}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  17.5.

Example 12

Sulfonamide 12: A solution of dibenzylphosphonate 6 (0.23 g, 0.29 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.5 mL) at  $0^\circ\text{C}$  was treated with trifluoroacetic acid (0.25 mL). The solution was stirred for 30 min at  $0^\circ\text{C}$  and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in  $\text{CH}_2\text{Cl}_2$  (3 mL) and cooled to  $0^\circ\text{C}$ .

Triethylamine (0.16 mL, 1.17 mmol) was added followed by the treatment of 4-fluorobenzenesulfonyl chloride (57 mg, 0.29 mmol). The solution was stirred for 1 h at  $0^\circ\text{C}$  and the product was partitioned between  $\text{CH}_2\text{Cl}_2$  and saturated  $\text{NaHCO}_3$ . The organic phase was washed with saturated NaCl, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the sulfonamide (0.13 g, 55%, GS 191482) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.81 (m, 2H), 7.38 (m, 10H), 7.24 (m, 2H), 7.12 (d,  $J = 8.1$  Hz, 2H), 6.82 (d,  $J = 8.4$  Hz, 2H), 5.65 (d,  $J = 5.4$  Hz, 1H), 5.17 (m, 4H), 5.0 (m, 1H), 4.90 (d, 1H), 4.20 (d,  $J = 9.9$  Hz, 2H), 3.97 (m, 1H), 3.86 (m, 3H), 3.73 (m, 2H), 3.6 (broad, s, 1H), 3.13 (m, 1H), 3.03-2.79 (m, 6H), 1.86 (m, 1H), 1.66-1.58 (m, 2H), 0.92 (d,  $J = 6.6$  Hz, 3H), 0.88 (d,  $J = 6.6$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.3.

Example 13

Phosphonic Acid 13: To a solution of 12 (70 mg, 0.083 mmol) in MeOH (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under  $\text{H}_2$  atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (49 mg, 90%, GS 191483) as a white solid:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.89 (m, 2H), 7.32 (m, 2H), 7.18 (d,  $J = 8.4$  Hz, 2H), 6.9 (d,  $J = 8.1$  Hz, 2H), 5.59 (d,  $J = 5.1$  Hz, 1H), 4.94 (m, 1H), 4.16 (d,  $J = 9.9$  Hz, 2H), 3.94 (m, 1H), 3.85-3.7 (m, 5H), 3.43 (dd, 1H), 3.15-2.87 (m, 5H), 2.48 (m, 1H), 2.03 (m, 1H), 1.59-1.36 (m, 2H), 0.93 (d,  $J = 6.3$  Hz, 3H), 0.87 (d,  $J = 6.3$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  17.5.

Example 14



Sulfonamide 14: A solution of dibenzylphosphonate 6 (0.21 g, 0.26 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.5 mL) at  $0^\circ\text{C}$  was treated with trifluoroacetic acid (0.25 mL). The solution was stirred for 30 min at  $0^\circ\text{C}$  and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in  $\text{CH}_2\text{Cl}_2$  (3 mL) and cooled to  $0^\circ\text{C}$ .

Triethylamine (0.15 mL, 1.04 mmol) was added followed by the treatment of 4-trifluoromethoxybenzenesulfonyl chloride (69 mg, 0.26 mmol). The solution was stirred for 1 h at  $0^\circ\text{C}$  and the product was partitioned between  $\text{CH}_2\text{Cl}_2$  and saturated  $\text{NaHCO}_3$ . The organic phase was washed with saturated NaCl, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the sulfonamide (0.17 g, 70%, GS 191508) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.84 (d,  $J$  = 9 Hz, 2H), 7.36 (m, 12H), 7.12 (d,  $J$  = 8.7 Hz, 2H), 6.81 (d,  $J$  = 8.7 Hz, 2H), 5.65 (d,  $J$  = 5.4 Hz, 1H), 5.16 (m, 4H), 5.03 (m, 1H), 4.89 (d, 1H), 4.2 (d,  $J$  = 9.9 Hz, 2H), 3.97 (m, 1H), 3.85 (m, 3H), 3.7 (m, 2H), 3.59 (broad, s, 1H), 3.18 (m, 1H), 3.1-3.0 (m, 3H), 2.96-2.78 (m, 3H), 1.86 (m, 1H), 1.66-1.5 (m, 2H), 0.93 (d,  $J$  = 6.6 Hz, 3H), 0.88 (d,  $J$  = 6.6 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.3.

#### Example 15

Phosphonic Acid 15: To a solution of 14 (70 mg, 0.083 mmol) in MeOH (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under  $\text{H}_2$  atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (50 mg, 90%, GS 192041) as a white solid:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.95 (dd, 2H), 7.49 (dd, 2H), 7.17 (dd, 2H), 6.92 (dd, 2H), 5.58 (d,  $J$  = 5.4 Hz, 1H), 4.89 (m, 1H), 4.17 (d,  $J$  = 9 Hz, 2H), 3.9 (m, 1H), 3.82-3.7 (m, 5H), 3.44 (m, 1H), 3.19-2.9 (m, 5H), 2.48 (m, 1H), 2.0 (m, 1H), 1.6 (m, 1H), 1.35 (m, 1H), 0.93 (d,  $J$  = 6.0 Hz, 3H), 0.88 (d,  $J$  = 6.0 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  17.4.

#### Example 16

Sulfonamide 16: A solution of dibenzylphosphonate 6 (0.59 g, 0.76 mmol) in  $\text{CH}_2\text{Cl}_2$  (2.0 mL) at  $0^\circ\text{C}$  was treated with trifluoroacetic acid (1.0 mL). The solution was stirred for 30 min at  $0^\circ\text{C}$  and then warmed to room temperature for an additional 30 min. The reaction

mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in  $\text{CH}_2\text{Cl}_2$  (3 mL) and cooled to  $0^\circ\text{C}$ .

Triethylamine (0.53 mL, 3.80 mmol) was added followed by the treatment of hydrogen chloride salt of 3-pyridinylsulfonyl chloride (0.17 g, 0.80 mmol, prepared according to Karaman, R. et al. J. Am. Chem. Soc. 1992, 114, 4889). The solution was stirred for 30 min at  $0^\circ\text{C}$  and warmed to room temperature for 30 min. The product was partitioned between  $\text{CH}_2\text{Cl}_2$  and saturated  $\text{NaHCO}_3$ . The organic phase was washed with saturated  $\text{NaCl}$ , dried with  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (4% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the sulfonamide (0.50 g, 80%, GS 273805) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  9.0 (d,  $J = 1.5$  Hz, 1H), 8.8 (dd, 1H), 8.05 (d,  $J = 8.7$  Hz, 1H), 7.48 (m, 1H), 7.36 (m, 10H), 7.12 (d,  $J = 8.4$  Hz, 2H), 6.82 (d,  $J = 9.0$  Hz, 2H), 5.65 (d,  $J = 5.1$  Hz, 1H), 5.18 (m, 4H), 5.06 (m, 1H), 4.93 (d, 1H), 4.21 (d,  $J = 8.4$  Hz, 2H), 3.97 (m, 1H), 3.86 (m, 3H), 3.74 (m, 2H), 3.2 (m, 1H), 3.1-2.83 (m, 5H), 2.76 (m, 1H), 1.88 (m, 1H), 1.62 (m, 2H), 0.92 (d,  $J = 6.3$  Hz, 3H), 0.88 (d,  $J = 6.3$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.3.

#### Example 17

Phosphonic Acid 17: To a solution of 16 (40 mg, 0.049 mmol) in MeOH (3 mL) and AcOH (1 mL) was added 10% Pd/C (10 mg). The suspension was stirred under  $\text{H}_2$  atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (28 mg, 90%, GS 273845) as a white solid:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  8.98 (s, 1H), 8.77 (broad s, 1H), 8.25 (dd, 1H), 7.6 (m, 1H), 7.15 (m, 2H), 6.90 (m, 2H), 5.6 (d,  $J = 5.4$  Hz, 1H), 4.98 (m, 1H), 4.15 (d, 2H), 3.97-3.7 (m, 6H), 3.45-2.89 (m, 6H), 2.50 (m, 1H), 2.0 (m, 1H), 1.6-1.35 (m, 2H), 0.9 (m, 6H).

#### Example 18

Sulfonamide 18: A solution of dibenzylphosphonate 6 (0.15 g, 0.19 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.60 mL) at  $0^\circ\text{C}$  was treated with trifluoroacetic acid (0.30 mL). The solution was stirred for 30 min at  $0^\circ\text{C}$  and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the

ammonium triflate salt which was dissolved in  $\text{CH}_2\text{Cl}_2$  (2 mL) and cooled to  $0^\circ\text{C}$ .

Triethylamine (0.11 mL, 0.76 mmol) was added followed by the treatment of 4-formylbenzenesulfonyl chloride (43 mg, 0.21 mmol). The solution was stirred for 30 min at  $0^\circ\text{C}$  and warmed to room temperature for 30 min. The product was partitioned between

5  $\text{CH}_2\text{Cl}_2$  and saturated  $\text{NaHCO}_3$ . The organic phase was washed with saturated  $\text{NaCl}$ , dried with  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the sulfonamide (0.13 g, 80%, GS 278114) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  10.1 (s, 1H), 8.04 (d,  $J$  = 8.1 Hz, 2H), 7.94 (d,  $J$  = 8.1 Hz, 2H), 7.35 (m, 10H), 7.13 (m,  $J$  = 8.1 Hz, 2H), 10 6.82 (d,  $J$  = 8.1 Hz, 2H), 5.65 (d,  $J$  = 5.4 Hz, 1H), 5.17 (m, 4H), 5.06 (m, 1H), 4.93 (m, 1H), 4.2 (d,  $J$  = 9.9 Hz, 2H), 3.94 (m, 1H), 3.85 (m, 3H), 3.7 (m, 2H), 3.18-2.87 (m, 5H), 2.78 (m, 1H), 1.86 (m, 1H), 1.67-1.58 (m, 2H), 0.93 (d,  $J$  = 6.6 Hz, 3H), 0.88 (d,  $J$  = 6.6 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.3.

#### 15 Example 19

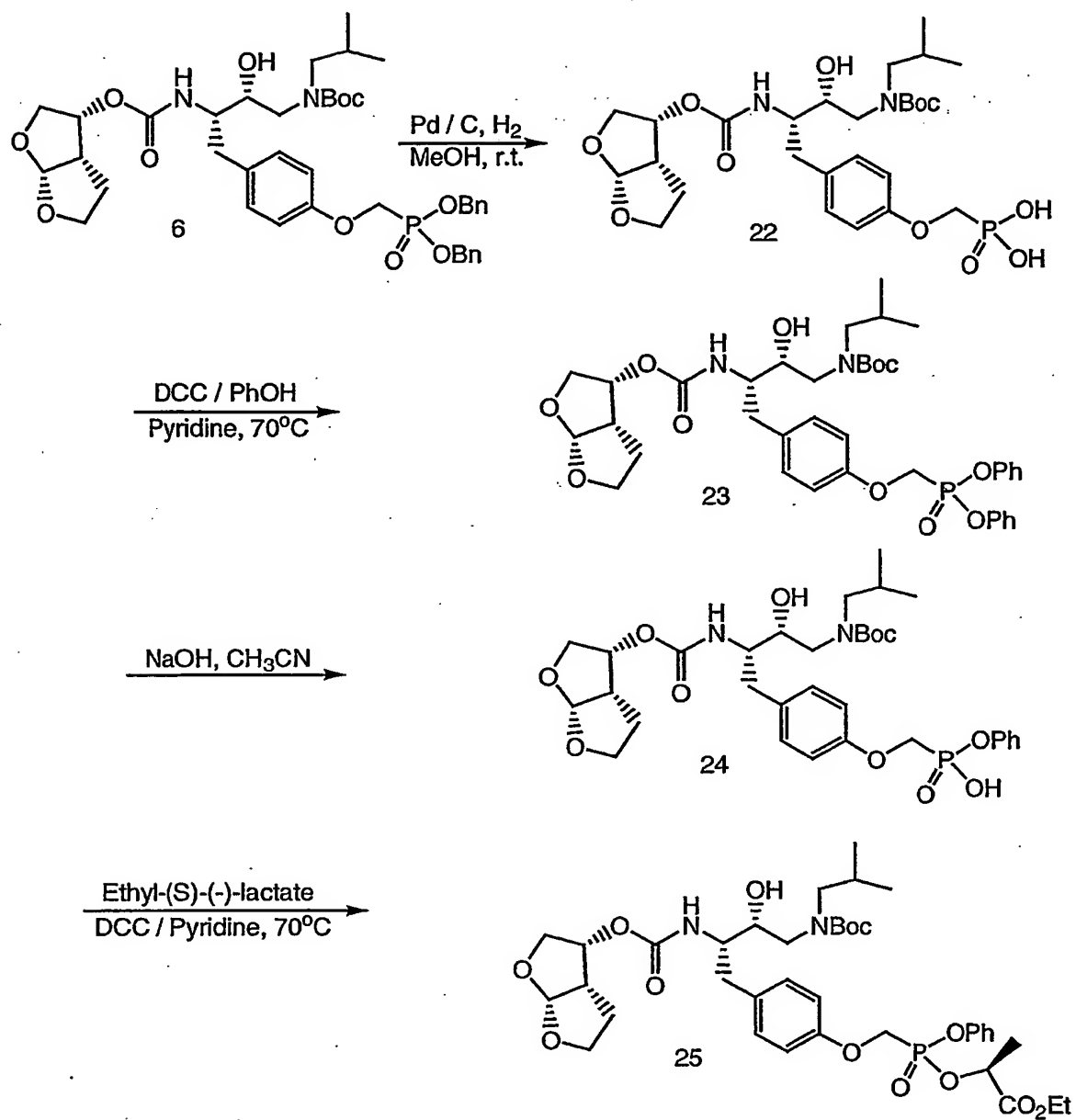
Phosphonic Acid 19: To a solution of 18 (0.12 g, 0.15 mmol) in EtOAc (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under  $\text{H}_2$  atmosphere (balloon) at room temperature for 6 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (93 mg, 95%) as a 20 white solid.

#### Example 20

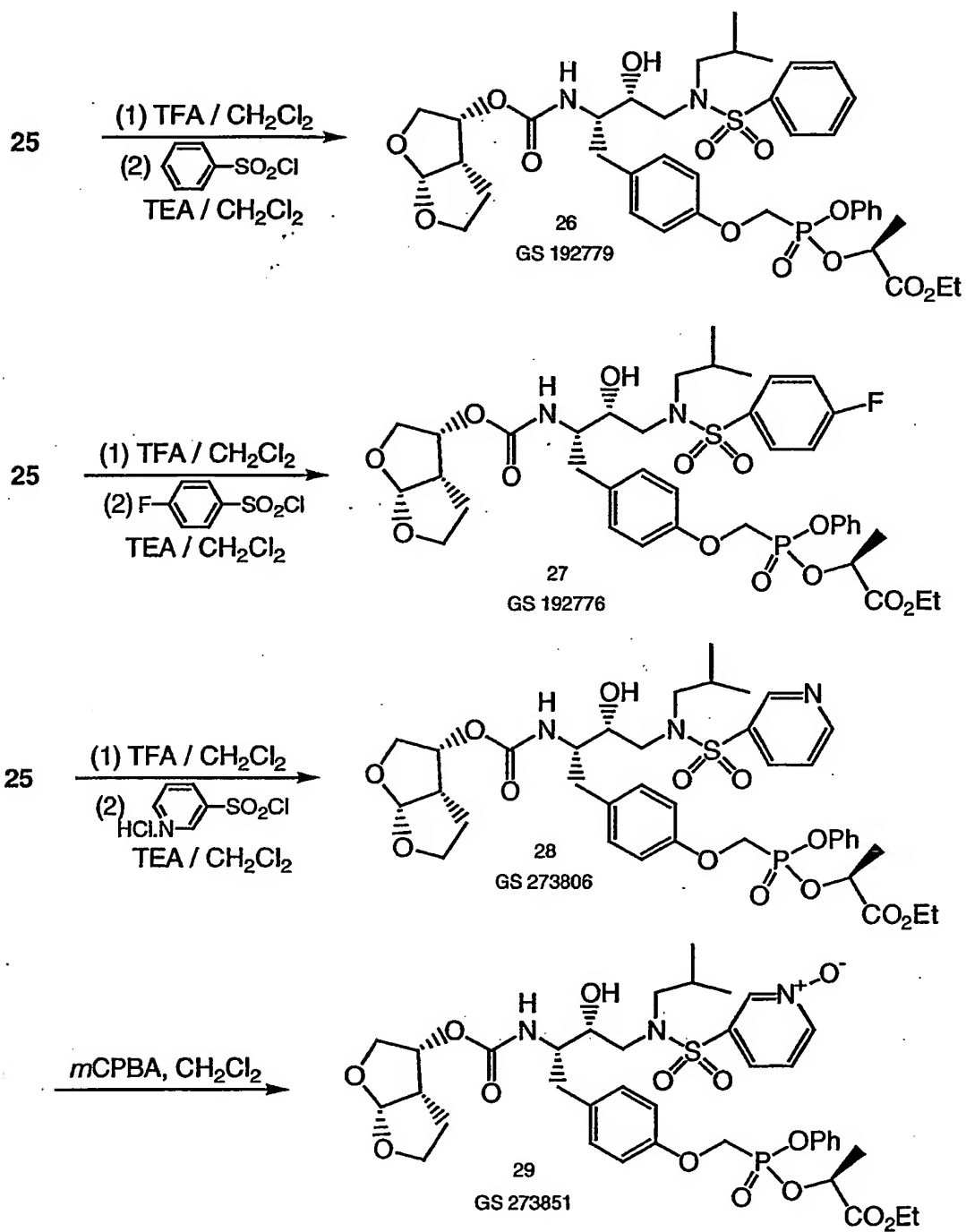
Phosphonic Acids 20 and 21: Compound 19 (93 mg, 0.14 mmol) was dissolved in  $\text{CH}_3\text{CN}$  (2 mL). *N,O*-Bis(trimethylsilyl)acetamide (BSA, 0.28 g, 1.4 mmol) was added. The reaction 25 mixture was heated to reflux for 1 h, cooled to room temperature and concentrated. The residue was co-evaporated with toluene and chloroform and dried under vacuum to give a semi-solid which was dissolved in EtOAc (2 mL). Morpholine (60  $\mu\text{L}$ , 0.9 mmol), AcOH (32  $\mu\text{L}$ , 0.56 mmol), and  $\text{NaBH}_3\text{CN}$  (17 mg, 0.28 mmol) were added and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with  $\text{H}_2\text{O}$ , stirred for 30 2 h, filtered, and concentrated. The crude product was purified by HPLC to give the phosphonic acid 20 (10 mg, GS 278118) as a white solid:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.80 (d,  $J$  = 7.8 Hz, 2H), 7.56 (d,  $J$  = 7.5 Hz, 2H), 7.17 (d,  $J$  = 7.8 Hz, 2H), 6.91 (d,  $J$  = 7.5 Hz, 2H), 5.59

(d, J = 5.1 Hz, 1H), 5.06 (m, 1H), 4.7 (s, 2H), 4.15 (d, J = 10.2 Hz, 2H), 3.92 (m, 1H), 3.82-3.7 (m, 5H), 3.43 (dd, 1H), 3.11-2.89 (m, 6H), 2.50 (m, 1H), 2.0 (m, 1H), 1.6-1.35 (m, 2H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  17.3. Phosphonic acid 21 (15 mg, GS 278117) as a white solid:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.8-7.7 (m, 4H), 7.20 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 5.62 (d, J = 5.1 Hz, 1H), 5.00 (m, 1H), 4.42 (s, 2H), 4.20 (dd, 2H), 3.98-3.68 (m, 9H), 3.3-2.92 (m, 11H), 2.6 (m, 1H), 2.0 (m, 1H), 1.6 (m, 2H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  16.2.

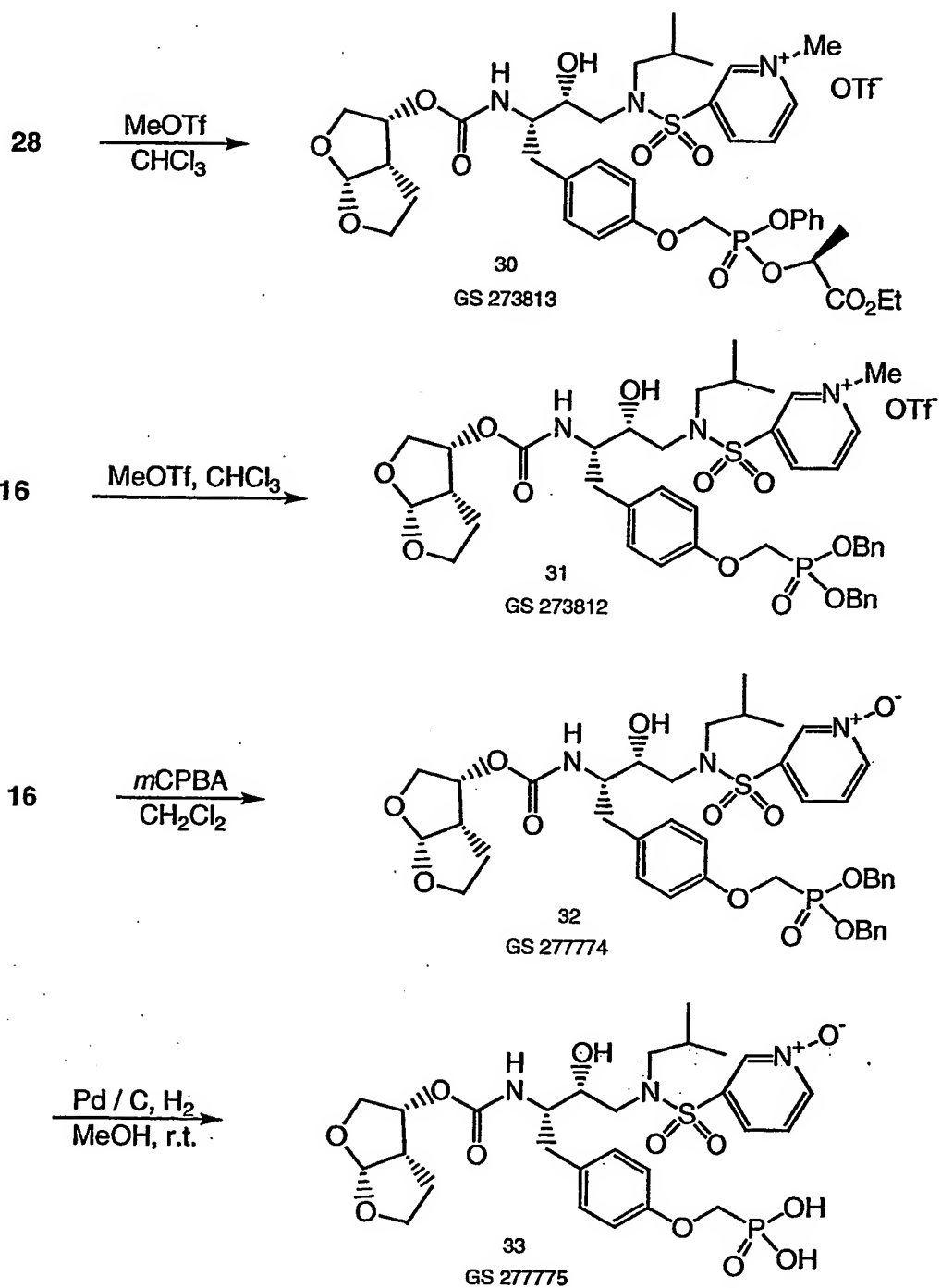
Scheme 6



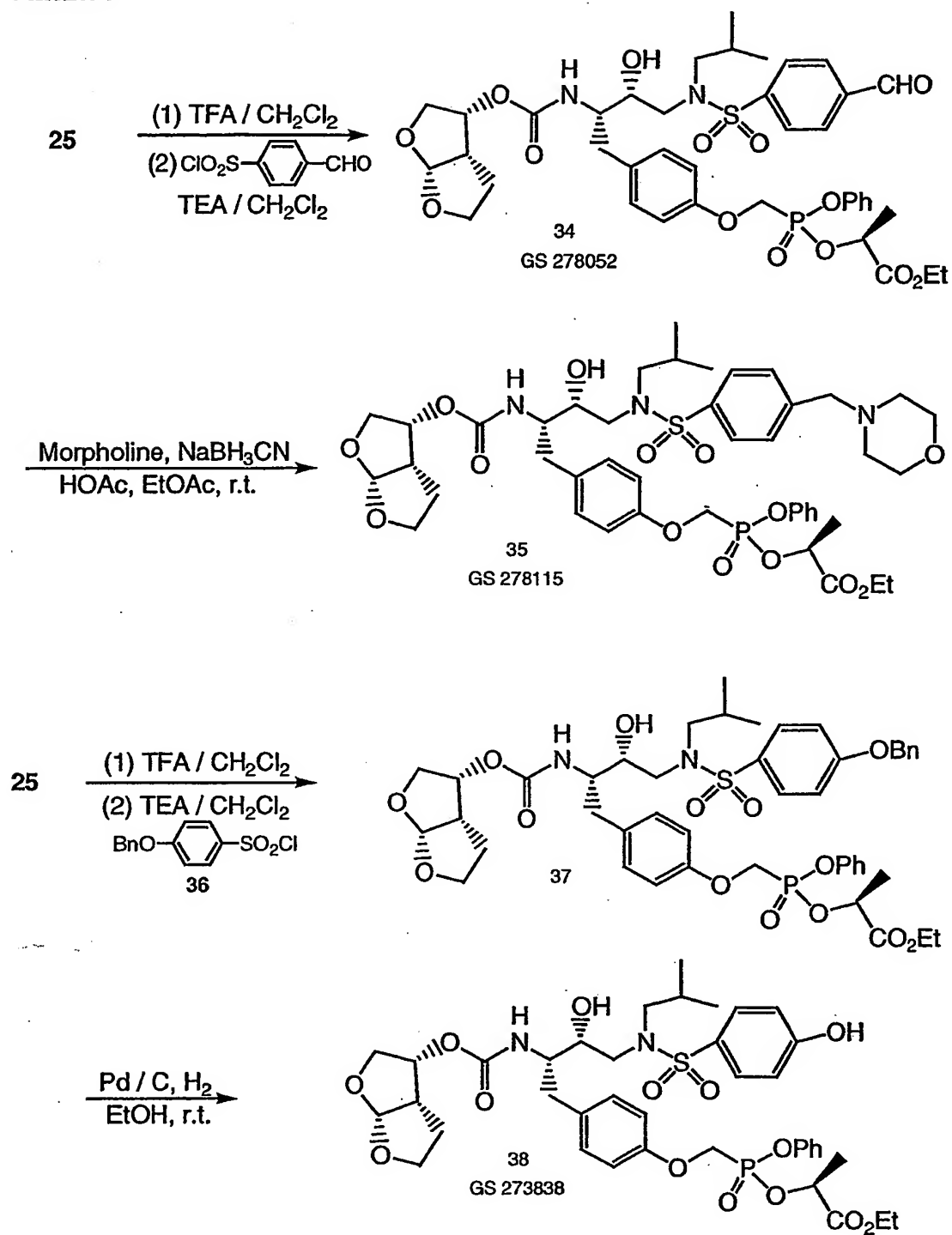
## Scheme 7



## Scheme 8

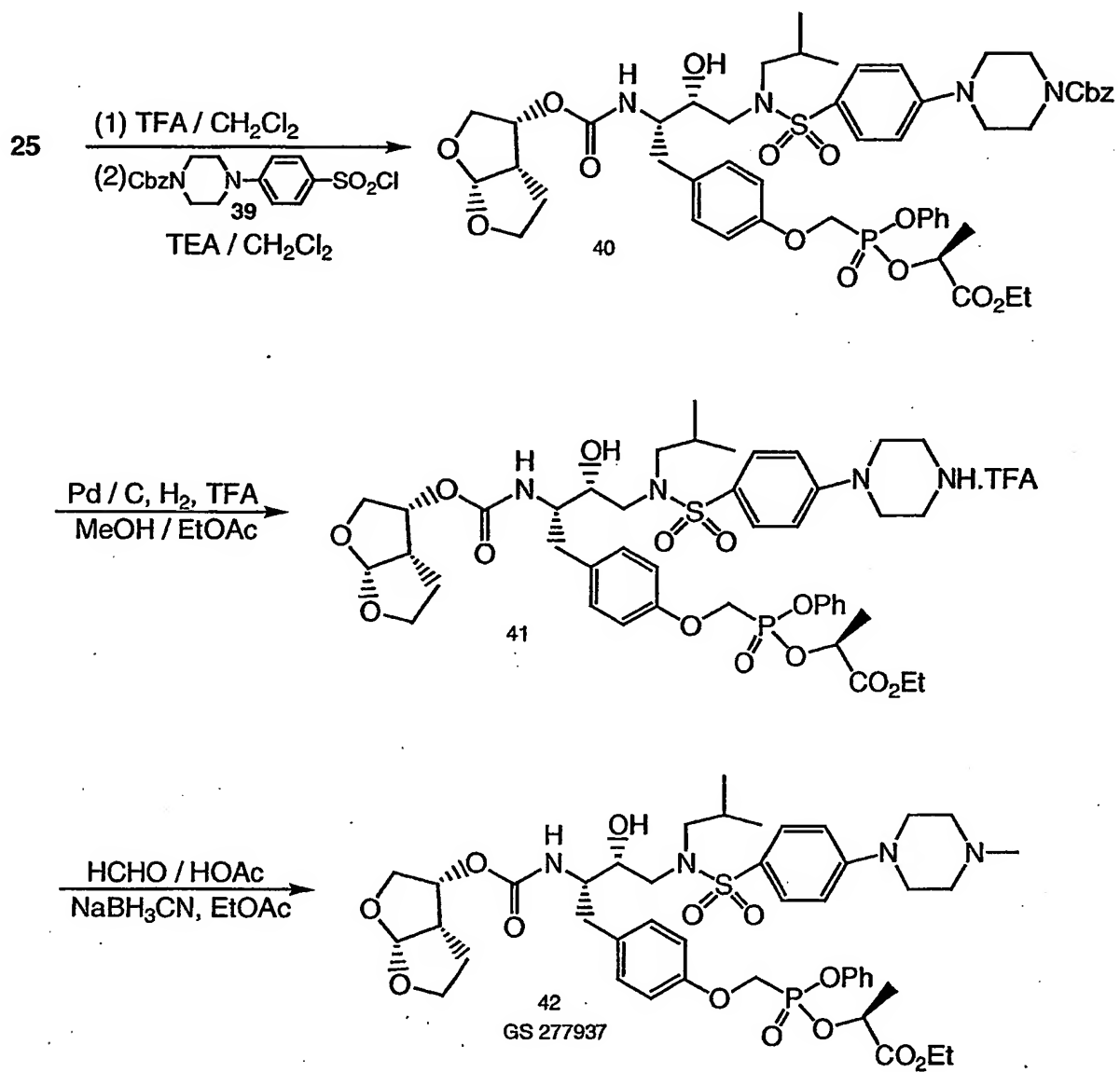


## Scheme 9

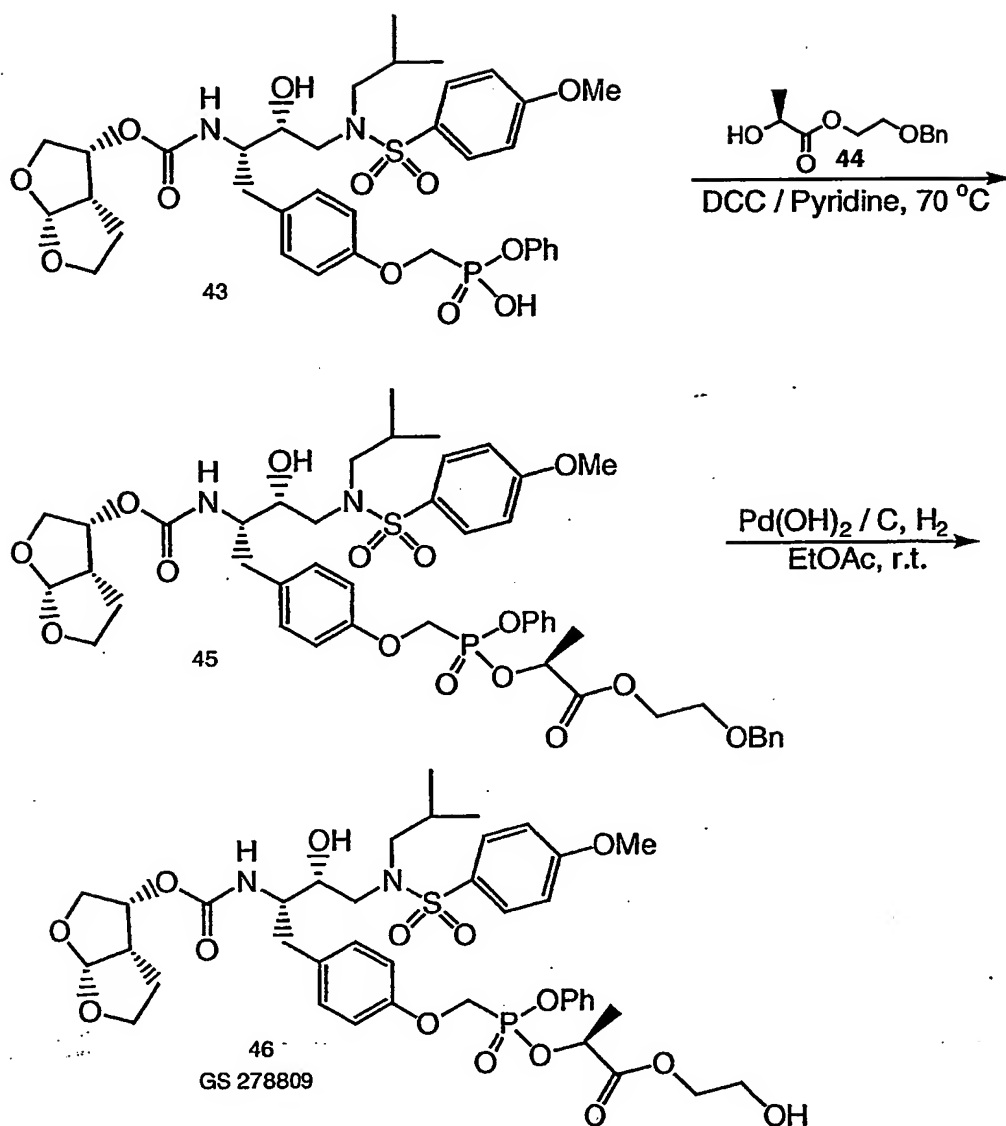




## Scheme 10



## Scheme 11

5 Example 21

Phosphonic Acid 22: To a solution of dibenzylphosphonate 6 (5.00 g, 6.39 mmol) in EtOH (100 mL) was added 10% Pd/C (1.4 g). The suspension was stirred under  $\text{H}_2$  atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid

10 (3.66 g, 95%) as a white solid.

Example 22

Diphenylphosphonate 23: A solution of 22 (3.65 g, 6.06 mmol) and phenol (5.70 g, 60.6 mmol) in pyridine (30 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (5.00 g, 24.24 mmol) was added. The reaction mixture was stirred at 70°C for 2 h and cooled to room temperature. EtOAc was added and the side product 1,3-dicyclohexyl urea was filtered off.

- 5 The filtrate was concentrated and dissolved in CH<sub>3</sub>CN (20 mL) at 0°C. The mixture was treated with DOWEX 50W x 8-400 ion-exchange resin and stirred for 30 min at 0°C. The resin was filtered off and the filtrate was concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the diphenylphosphonate (2.74 g, 60%) as a white solid.

10

#### Example 23

Monophosphonic Acid 24: To a solution of 23 (2.74 g, 3.63 mmol) in CH<sub>3</sub>CN (40 mL) at 0°C was added 1 N NaOH (9.07 mL, 9.07 mmol). The reaction mixture was stirred at 0°C for 1 h. DOWEX 50W x 8-400 ion-exchange resin was added and the reaction mixture was

- 15 stirred for 30 min at 0°C. The resin was filtered off and the filtrate was concentrated and co-evaporated with toluene. The crude product was triturated with EtOAc/hexane (1/2) to give the monophosphonic acid (2.34 g, 95%) as a white solid.

#### Example 24

- 20 Monophospholactate 25: A solution of 24 (2.00 g, 2.95 mmol) and ethyl-(S)-(-)-lactate (1.34 mL, 11.80 mmol) in pyridine (20 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (2.43 g, 11.80 mmol) was added. The reaction mixture was stirred at 70°C for 2 h and cooled to room temperature. The solvent was removed under reduced pressure. The residue was suspended in EtOAc and 1,3-dicyclohexyl urea was filtered off. The product was partitioned
- 25 between EtOAc and 0.2 N HCl. The EtOAc layer was washed with 0.2 N HCl, H<sub>2</sub>O, saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the monophospholactate (1.38 g, 60%) as a white solid.

#### Example 25

Monophospholactate 26: A solution of 25 (0.37 g, 0.48 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.80 mL) at 0°C was treated with trifluoroacetic acid (0.40 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was

diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in  $\text{CH}_2\text{Cl}_2$  (3 mL) and cooled to  $0^\circ\text{C}$ .

Triethylamine (0.27 mL, 1.92 mmol) was added followed by the treatment of

- 5 benzenesulfonyl chloride (84 mg, 0.48 mmol). The solution was stirred for 30 min at  $0^\circ\text{C}$  and then warmed to room temperature for 30 min. The product was partitioned between  $\text{CH}_2\text{Cl}_2$  and 0.2 N HCl. The organic phase was washed with saturated NaCl, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the
- 10 monophospholactate (0.33 g, 85%, GS 192779, 1:1 diastereomeric mixture) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.78 (dd, 2H), 7.59 (m, 3H), 7.38-7.18 (m, 7H), 6.93 (dd, 2H), 5.66 (m, 1H), 5.18-4.93 (m, 3H), 4.56-4.4 (m, 2H), 4.2 (m, 2H), 4.1-3.7 (m, 6H), 3.17 (m, 1H), 3.02-2.8 (m, 6H), 1.84 (m, 1H), 1.82-1.5 (m, 5H), 1.27 (m, 3H), 0.93 (d,  $J = 6.3$  Hz, 3H), 0.88 (d,  $J = 6.3$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.4, 15.3.

15

#### Example 26

Monophospholactate 27: A solution of 25 (0.50 g, 0.64 mmol) in  $\text{CH}_2\text{Cl}_2$  (1.0 mL) at  $0^\circ\text{C}$  was treated with trifluoroacetic acid (0.5 mL). The solution was stirred for 30 min at  $0^\circ\text{C}$  and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted

20 with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in  $\text{CH}_2\text{Cl}_2$  (4 mL) and cooled to  $0^\circ\text{C}$ . Triethylamine (0.36 mL, 2.56 mmol) was added followed by the treatment of 4-fluorobenzenesulfonyl chloride (0.13 g, 0.64 mmol). The solution was stirred for 30 min at  $0^\circ\text{C}$  and then warmed to room

25 temperature for 30 min. The product was partitioned between  $\text{CH}_2\text{Cl}_2$  and 0.2 N HCl. The organic phase was washed with saturated NaCl, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the monophospholactate (0.44 g, 81%, GS 192776, 3/2 diastereomeric mixture) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.80 (m, 2H), 7.38-7.15 (m, 9H), 6.92 (m, 2H), 5.66 (m, 1H), 5.2-4.9 (m, 3H), 4.57-4.4 (m, 2H), 4.2 (m, 2H), 4.1-3.7 (m, 6H), 3.6 (broad, s, 1H), 3.17 (m, 1H), 3.02-2.75 (m, 6H), 1.85 (m, 1H), 1.7-1.5 (m, 5H), 1.26 (m, 3H), 0.93 (d,  $J = 6.3$  Hz, 3H), 0.88 (d,  $J = 6.3$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.3, 15.2.

30

Example 27

Monophospholactate 28: A solution of 25 (0.50 g, 0.64 mmol) in  $\text{CH}_2\text{Cl}_2$  (1.0 mL) at  $0^\circ\text{C}$  was treated with trifluoroacetic acid (0.5 mL). The solution was stirred for 30 min at  $0^\circ\text{C}$  and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in  $\text{CH}_2\text{Cl}_2$  (3 mL) and cooled to  $0^\circ\text{C}$ . Triethylamine (0.45 mL, 3.20 mmol) was added followed by the treatment of hydrogen chloride salt of 3-pyridinylsulfonyl chloride (0.14 g, 0.65 mmol). The solution was stirred for 30 min at  $0^\circ\text{C}$  and then warmed to room temperature for 30 min. The product was partitioned between  $\text{CH}_2\text{Cl}_2$  and  $\text{H}_2\text{O}$ . The organic phase was washed with saturated NaCl, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (4% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the monophospholactate (0.41 g, 79%, GS 273806, 1:1 diastereomeric mixture) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  9.0 (s, 1H), 8.83 (dd, 1H), 8.06 (d,  $J = 7.8$  Hz, 1H), 7.5 (m, 1H), 7.38-7.15 (m, 7H), 6.92 (m, 2H), 5.66 (m, 1H), 5.18-4.95 (m, 3H), 4.6-4.41 (m, 2H), 4.2 (m, 2H), 4.0 (m, 1H), 3.95-3.76 (m, 6H), 3.23-2.8 (m, 7H), 1.88 (m, 1H), 1.7-1.5 (m, 5H), 1.26 (m, 3H), 0.93 (d,  $J = 6.6$  Hz, 3H), 0.83 (d,  $J = 6.6$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.3, 15.3.

20 Example 28

Monophospholactate 29: A solution of compound 28 (0.82 g, 1.00 mmol) in  $\text{CH}_2\text{Cl}_2$  (8 mL) at  $0^\circ\text{C}$  was treated with *m*CPBA (1.25 eq). The solution was stirred for 1 h at  $0^\circ\text{C}$  and then warmed to room temperature for an additional 6 h. The reaction mixture was partitioned between  $\text{CH}_2\text{Cl}_2$  and saturated  $\text{NaHCO}_3$ . The organic phase was washed with saturated NaCl, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (10% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the monophospholactate (0.59 g, 70%, GS 273851, 1:1 diastereomeric mixture) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.63 (dd, 1H), 8.3 (dd, 1H), 7.57 (m, 1H), 7.44 (m, 1H), 7.38-7.13 (m, 7H), 6.92 (m, 2H), 5.66 (m, 1H), 5.2-5.05 (m, 2H), 4.57-4.4 (m, 2H), 4.2 (m, 2H), 4.0-3.73 (m, 6H), 3.2 (m, 2H), 3.0 (m, 4H), 2.77 (m, 1H), 1.92 (m, 1H), 1.7-1.49 (m, 5H), 1.26 (m, 3H), 0.91 (m, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.3, 15.3.

Example 29

Monophospholactate 30: A solution of compound 28 (71 mg, 0.087 mmol) in  $\text{CHCl}_3$  (1 mL) was treated with MeOTf (18 mg, 0.11 mmol). The solution was stirred at room temperature for 1 h. The reaction mixture was concentrated and co-evaporated with toluene (2 x),  $\text{CHCl}_3$  (2 x) and dried under vacuum to give the monophospholactate (81 mg, 95%, GS 273813, 1:1 diastereomeric mixture) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  9.0 (dd, 1H), 8.76 (m, 2H), 8.1 (m, 1H), 7.35-7.1 (m, 7H), 6.89 (m, 2H), 5.64 (m, 1H), 5.25-5.0 (m, 3H), 4.6-4.41 (m, 5H), 4.2 (m, 2H), 3.92-3.72 (m, 6H), 3.28 (m, 2H), 3.04-2.85 (m, 3H), 2.62 (m, 1H), 1.97 (m, 1H), 1.62-1.5 (m, 5H), 1.25 (m, 3H), 0.97 (m, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.4, 15.4.

#### 10 Example 30

Dibenzylphosphonate 31: A solution of compound 16 (0.15 g, 0.18 mmol) in  $\text{CHCl}_3$  (2 mL) was treated with MeOTf (37 mg, 0.23 mmol). The solution was stirred at room temperature for 2 h. The reaction mixture was concentrated and co-evaporated with toluene (2 x),  $\text{CHCl}_3$  (2 x) and dried under vacuum to give the dibenzylphosphonate (0.17 g, 95%, GS 273812) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  9.0 (dd, 1H), 8.73 (m, 2H), 8.09 (m, 1H), 7.35 (m, 10H), 7.09 (d,  $J$  = 8.4 Hz, 2H), 6.79 (d,  $J$  = 8.1 Hz, 2H), 5.61 (d,  $J$  = 4.2 Hz, 1H), 5.2-4.96 (m, 6H), 4.54 (s, 3H), 4.2 (dd, 2H), 3.92-3.69 (m, 6H), 3.3 (m, 2H), 3.04-2.6 (m, 5H), 1.97 (m, 1H), 1.6 (m, 2H), 0.98 (m, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.4.

#### 20 Example 31

Dibenzylphosphonate 32: A solution of compound 16 (0.15 g, 0.18 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 mL) at  $0^\circ\text{C}$  was treated with *m*CPBA (1.25 eq). The solution was stirred for 1 h at  $0^\circ\text{C}$  and then warmed to room temperature overnight. The reaction mixture was partitioned between 10% 2-propanol/ $\text{CH}_2\text{Cl}_2$  and saturated  $\text{NaHCO}_3$ . The organic phase was washed with saturated NaCl, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (10% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the dibenzylphosphonate (0.11 g, 70%, GS 277774) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.64 (m, 1H), 8.27 (d,  $J$  = 6.9 Hz, 1H), 7.57 (d,  $J$  = 8.4 Hz, 1H), 7.36 (m, 11H), 7.10 (d,  $J$  = 8.4 Hz, 2H), 6.81 (d,  $J$  = 8.7 Hz, 2H), 5.65 (d,  $J$  = 5.4 Hz, 1H), 5.22-5.02 (m, 6H), 4.21 (dd, 2H), 3.99-3.65 (m, 6H), 3.2 (m, 2H), 3.03-2.73 (m, 5H), 1.90 (m, 1H), 1.66-1.56 (m, 2H), 0.91 (m, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.3.

Example 32

Phosphonic Acid 33: To a solution of dibenzylphosphonate 32 (0.1 g, 0.12 mmol) in MeOH (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H<sub>2</sub> atmosphere (balloon) at room temperature for 1 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and purified by HPLC to give the phosphonic acid (17 mg, GS 277775) as a white solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 8.68 (s, 1H), 8.47 (d, J = 6.0 Hz, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.68 (m, 1H), 7.14 (m, 2H), 6.90 (d, J = 7.8 Hz, 2H), 5.58 (d, J = 5.4 Hz, 1H), 5.00 (m, 1H), 4.08 (d, J = 9.9 Hz, 2H), 3.93-3.69 (m, 6H), 3.4-2.9 (m, 7H), 2.5 (m, 1H), 2.04 (m, 1H), 1.6-1.35 (m, 2H), 0.92 (m, 6H); <sup>31</sup>P NMR (CD<sub>3</sub>OD) δ 15.8.

Example 33

Monophospholactate 34: A solution of 25 (2.50 g, 3.21 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5.0 mL) at 0°C was treated with trifluoroacetic acid (2.5 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) and cooled to 0°C. Triethylamine (1.79 mL, 12.84 mmol) was added followed by the treatment of 4-formylbenzenesulfonyl chloride (0.72 g, 3.53 mmol) and the solution was stirred at 0°C for 1 h. The product was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and 5% HCl. The organic phase was washed with H<sub>2</sub>O, saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the monophospholactate (2.11 g, 77%, GS 278052, 1:1 diastereomeric mixture) as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 10.12 (s, 1H), 8.05 (d, J = 8.7 Hz, 2H), 7.95 (d, J = 7.5 Hz, 2H), 7.38-7.15 (m, 7H), 6.94 (m, 2H), 5.67 (m, 1H), 5.18-4.91 (m, 3H), 4.57-4.4 (m, 2H), 4.2 (m, 2H), 4.0-3.69 (m, 6H), 3.57 (broad s, 1H), 3.19-2.8 (m, 7H), 1.87 (m, 1H), 1.69-1.48 (m, 5H), 1.25 (m, 3H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 17.3, 15.2.

Example 34

Monophospholactate 35: A solution of 34 (0.60 g, 0.71 mmol) and morpholine (0.31 mL, 3.54 mmol) in EtOAc (8 mL) was treated with HOAc (0.16 mL, 2.83 mmol) and NaBH<sub>3</sub>CN (89 mg, 1.42 mmol). The reaction mixture was stirred at room temperature for 4 h. The

product was partitioned between EtOAc and H<sub>2</sub>O. The organic phase was washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (6% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the monophospholactate (0.46 g, 70%, GS 278115, 1:1 diastereomeric mixture) as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.74 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.38-7.15 (m, 7H), 6.92 (m, 2H), 5.66 (m, 1H), 5.2-5.0 (m, 2H), 4.57-4.4 (m, 2H), 4.2 (m, 2H), 3.97-3.57 (m, 12H), 3.2-2.78 (m, 7H), 2.46 (broad, s, 4H), 1.87 (m, 1H), 1.64-1.5 (m, 5H), 1.25 (m, 3H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 17.3, 15.3.

#### 10 Example 35

Monophospholactate 37: A solution of 25 (0.50 g, 0.64 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) at 0°C was treated with trifluoroacetic acid (1 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) and cooled to 0°C. Triethylamine (0.45 mL, 3.20 mmol) was added followed by the treatment of 4-benzyloxybenzenesulfonyl chloride (0.18 g, 0.64 mmol, prepared according to Toja, E. et al. Eur. J. Med. Chem. 1991, 26, 403). The solution was stirred for 30 min at 0°C and then warmed to room temperature for 30 min. The product was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and 0.1 N HCl. The organic phase was washed with saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (4% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the monophospholactate (0.51 g, 85%) as a white solid.

#### 25 Example 36

Monophospholactate 38: To a solution of 37 (0.48 g, 0.52 mmol) in EtOH (15 mL) was added 10% Pd/C (0.10 g). The suspension was stirred under H<sub>2</sub> atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and the crude product was purified by column chromatography on silica gel (5% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the monophospholactate (0.38 g, 88%, GS 273838, 1:1 diastereomeric mixture) as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.86 (dd, 1H), 7.42-7.25 (m, 9H), 6.91 (m, 4H), 5.73 (d, J = 5.1 Hz, 1H), 5.42 (m, 1H), 5.18 (m, 2H), 4.76-4.31 (m, 2H), 4.22 (m, 2H), 4.12-3.75 (m, 6H), 3.63 (broad, s, 1H), 3.13 (m, 3H), 2.87 (m, 1H), 2.63



(m, 1H), 2.4 (m, 1H), 2.05 (m, 2H), 1.9 (m, 1H), 1.8(m, 1H), 1.6 (m, 3H), 1.25 (m, 3H), 0.95 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 6.6 Hz, 3H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 17.1, 15.7.

#### Example 37

- 5 Monophospholactate 40: A solution of 25 (0.75 g, 0.96 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) at 0°C was treated with trifluoroacetic acid (1 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt
- 10 which was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) and cooled to 0°C. Triethylamine (0.67 mL, 4.80 mmol) was added followed by the treatment of 4-(4'-benzyloxycarbonyl piperazinyl)benzenesulfonyl chloride (0.48 g, 1.22 mmol, prepared according to Toja, E. et al. *Arzneim. Forsch.* 1994, 44, 501). The solution was stirred at 0°C for 1 h and then warmed to room temperature for 30 min. The product was partitioned between 10% 2-
- 15 propanol/CH<sub>2</sub>Cl<sub>2</sub> and 0.1 N HCl. The organic phase was washed with saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the monophospholactate (0.63 g, 60%) as a white solid.

#### Example 38

- 20 Monophospholactate 41: To a solution of 40 (0.62 g, 0.60 mmol) in MeOH (8 mL) and EtOAc (2 mL) was added 10% Pd/C (0.20 g). The suspension was stirred under H<sub>2</sub> atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was treated with 1.2 equivalent of TFA, co-evaporated
- 25 with CHCl<sub>3</sub> and dried under vacuum to give the monophospholactate (0.55 g, 90%) as a white solid.

#### Example 39

- Monophospholactate 42: A solution of 41 (0.54 g, 0.53 mmol) and formaldehyde (0.16 mL, 5.30 mmol) in EtOAc (10 mL) was treated with HOAc (0.30 mL, 5.30 mmol) and NaBH<sub>3</sub>CN (0.33 g, 5.30 mmol). The reaction mixture was stirred at room temperature overnight. The product was partitioned between EtOAc and H<sub>2</sub>O. The organic phase was washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column
- 30

chromatography on silica gel (6% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the monophospholactate (97.2 mg, 20%, GS 277937, 1:1 diastereomeric mixture) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.64 (d,  $J = 9.0$  Hz, 2H), 7.38-7.17 (m, 7H), 6.95-6.88 (m, 4H), 5.67 (m, 1H), 5.2-4.96 (m, 2H), 4.57-4.4 (m, 2H), 4.2 (m, 2H), 3.97-3.64 (m, 8H), 3.49-3.37 (m, 4H), 3.05-2.78 (m, 12H), 1.88-1.62 (m, 3H), 1.58 (m, 3H), 1.25 (m, 3H), 0.93 (d,  $J = 6.3$  Hz, 3H), 0.88 (d,  $J = 6.3$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.3, 15.3.

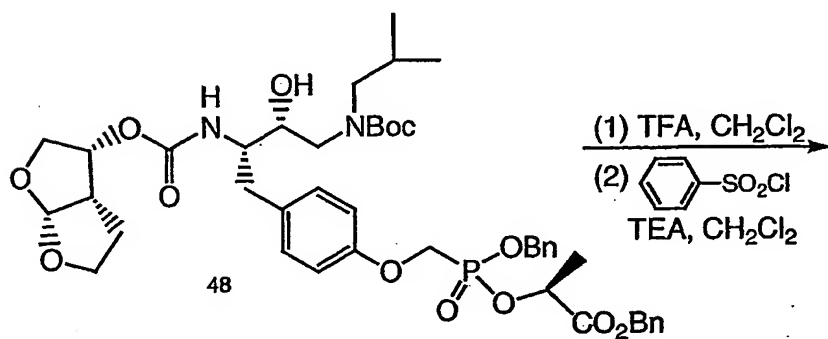
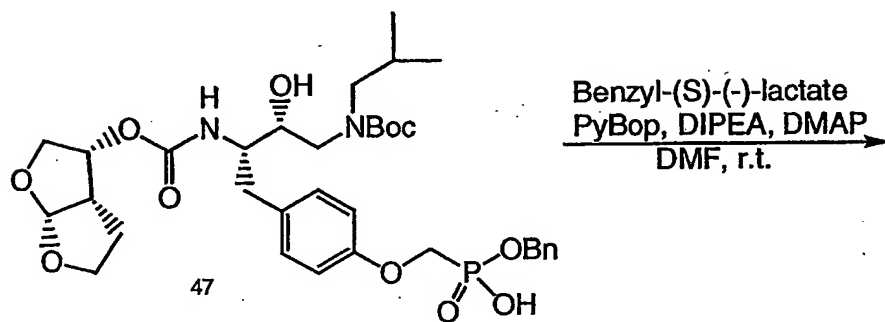
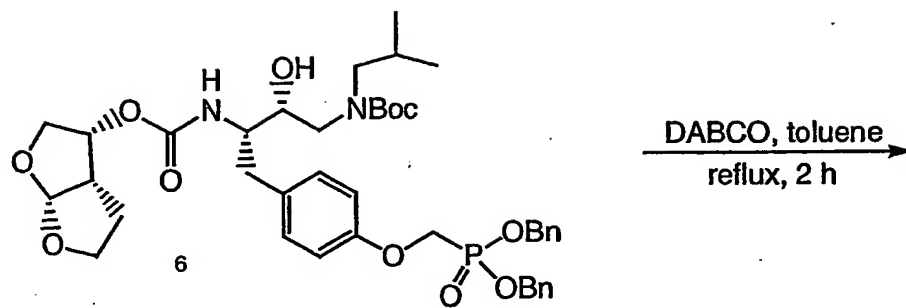
#### Example 40

Monophospholactate 45: A solution of 43 (0.12 g, 0.16 mmol) and lactate 44 (0.22 g, 1.02 mmol) in pyridine (1 mL) was heated to  $70^\circ\text{C}$  and 1,3-dicyclohexylcarbodiimide (0.17 g, 0.83 mmol) was added. The reaction mixture was stirred at  $70^\circ\text{C}$  for 4 h and cooled to room temperature. The solvent was removed under reduced pressure. The residue was suspended in EtOAc and 1,3-dicyclohexyl urea was filtered off. The product was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with 0.2 N HCl,  $\text{H}_2\text{O}$ , saturated NaCl, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the monophospholactate (45 mg, 26%) as a white solid.

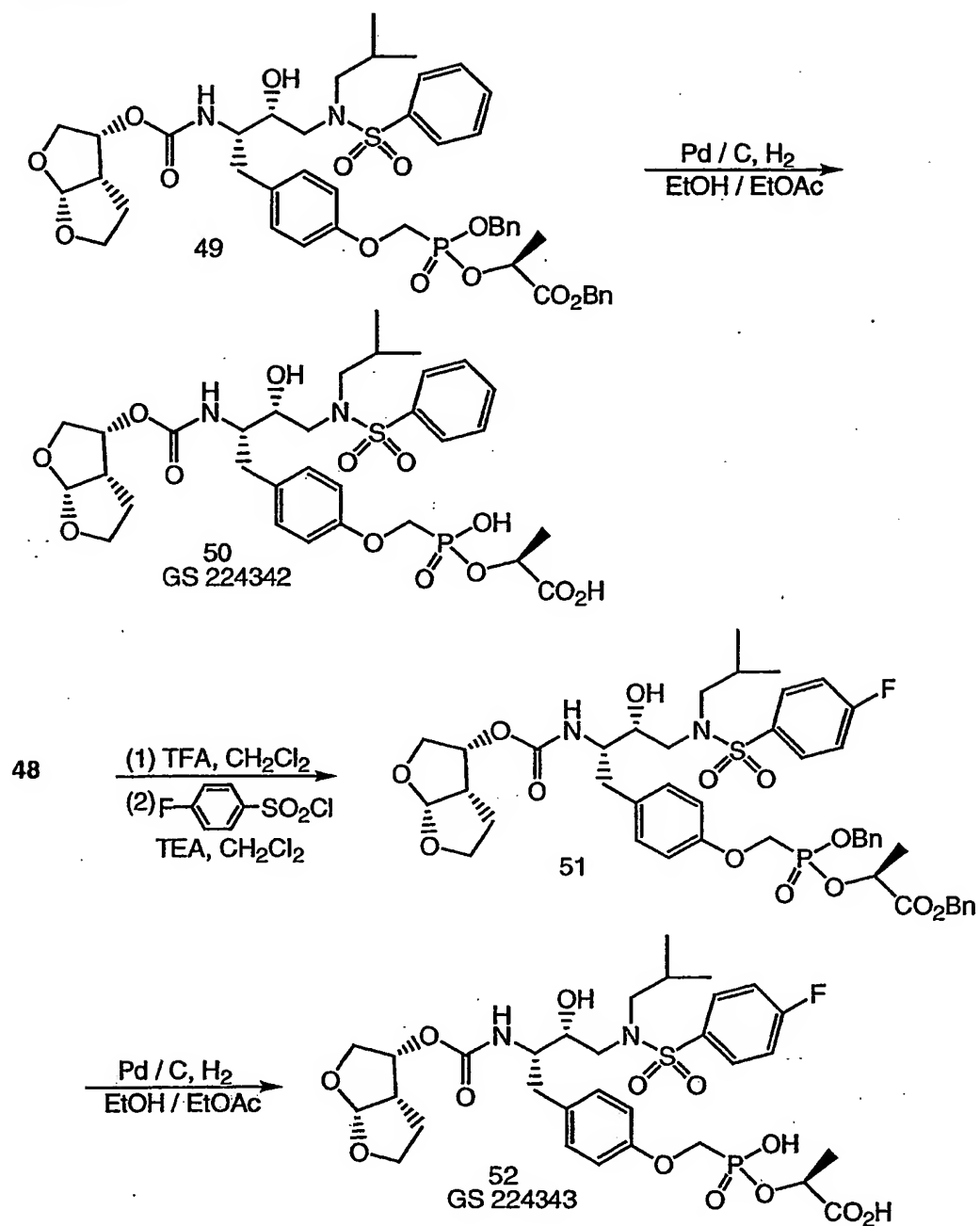
#### Example 41

Alcohol 46: To a solution of 45 (40 mg, 0.042 mmol) in EtOAc (2 mL) was added 20%  $\text{Pd}(\text{OH})_2/\text{C}$  (10 mg). The suspension was stirred under  $\text{H}_2$  atmosphere (balloon) at room temperature for 3 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and the product was dried under vacuum to give the alcohol (33 mg, 90%, GS 278809, 3/2 diastereomeric mixture) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.72 (d,  $J = 8.7$  Hz, 2H), 7.39-7.15 (m, 7H), 7.02-6.88 (m, 4H), 5.66 (d,  $J = 4.5$  Hz, 1H), 5.13-5.02 (m, 2H), 4.54-4.10 (m, 4H), 4.00-3.69 (m, 11H), 3.14 (m, 1H), 3.02-2.77 (m, 6H), 1.85-1.6 (m, 6H), 0.94 (d,  $J = 6.3$  Hz, 3H), 0.89 (d,  $J = 6.3$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.4, 15.9.

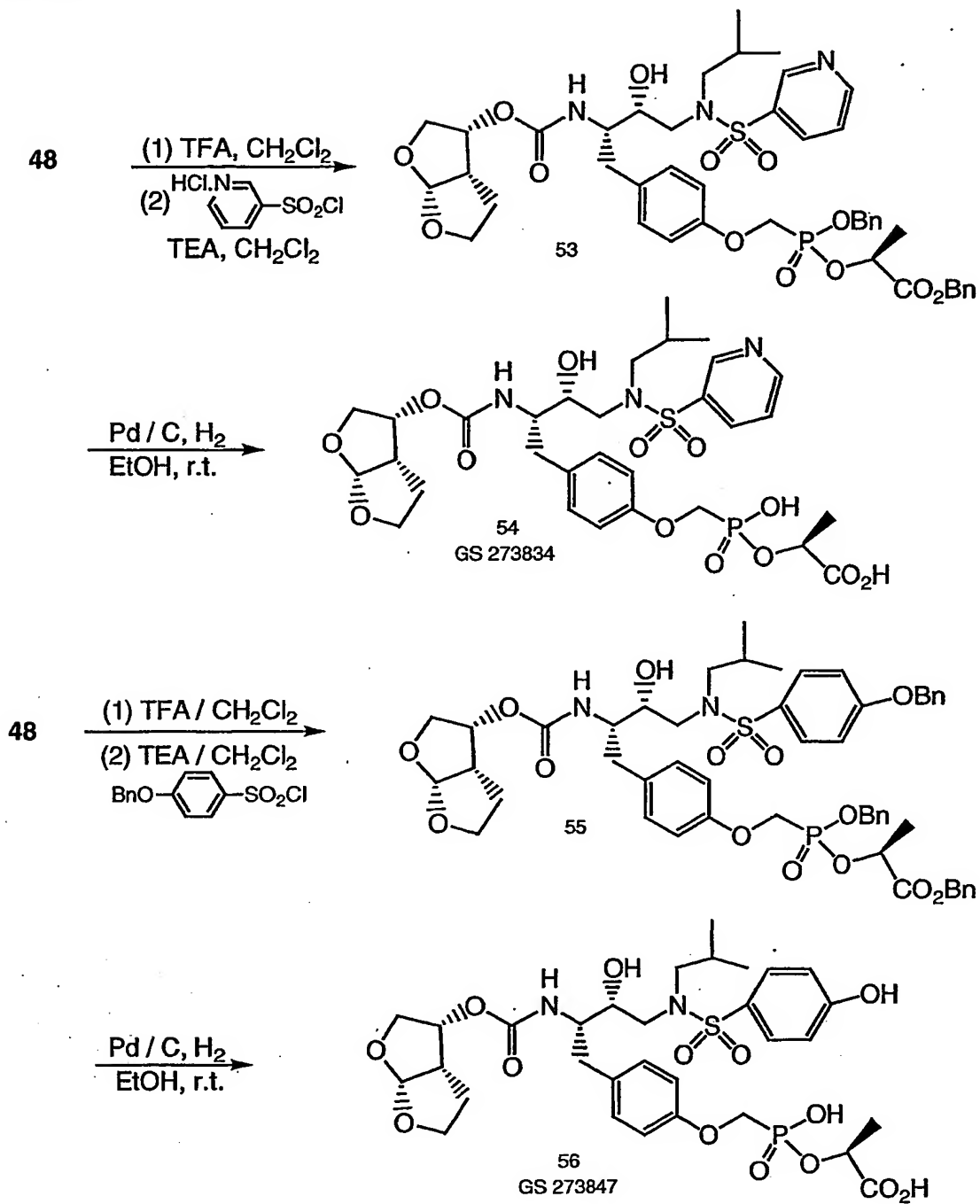
Scheme 12



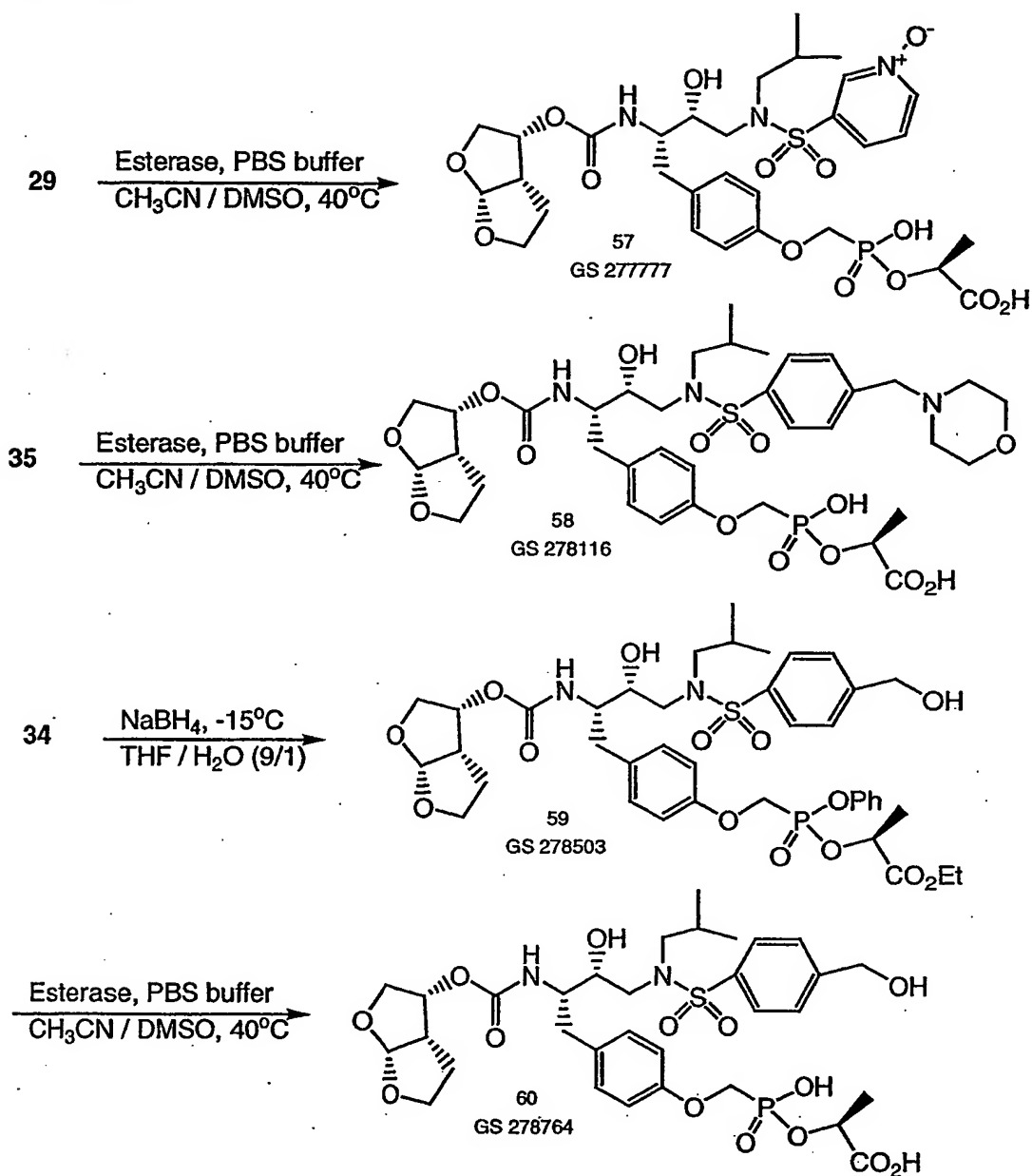
## Scheme 13



## Scheme 14



## Scheme 15

Example 42

- 5 Monobenzylphosphonate 47: A solution of 6 (2.00 g, 2.55 mmol) and DABCO (0.29 g, 2.55 mmol) in toluene (10 mL) was heated to reflux for 2 h. The solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with H<sub>2</sub>O, saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated.

The crude product was dried under vacuum to give the monobenzylphosphonate (1.68 g, 95%) as a white solid.

#### Example 43

- 5 Monophospholactate 48: To a solution of 47 (2.5 g, 3.61 mmol) and benzyl-(S)-(-)-lactate (0.87 mL, 5.42 mmol) in DMF (12 mL) was added PyBop (2.82 g, 5.42 mmol) and *N,N*-diisopropylethylamine (2.51 mL, 14.44 mmol). The reaction mixture was stirred at room temperature for 3 h and concentrated. The residue was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with H<sub>2</sub>O, saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered,  
10 and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the monophospholactate (1.58 g, 51%) as a white solid.

#### Example 44

- Monophospholactate 49: A solution of 48 (0.30 g, 0.35 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.6 mL) at 0°C  
15 was treated with trifluoroacetic acid (0.3 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and cooled to 0°C. Triethylamine (0.20 mL, 1.40  
20 mmol) was added followed by the treatment of benzenesulfonyl chloride (62 mg, 0.35 mmol). The solution was stirred at 0°C for 30 min and then warmed to room temperature for 30 min. The product was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and 0.1 N HCl. The organic phase was washed with saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the  
25 monophospholactate (0.17 g, 53%) as a white solid.

#### Example 45

- Metabolite X 50: To a solution of 49 (80 mg, 0.09 mmol) in EtOH (6 mL) and EtOAc (2 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H<sub>2</sub> atmosphere  
30 (balloon) at room temperature for 8 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated, co-evaporated with CHCl<sub>3</sub> and dried under vacuum to give the metabolite X (61 mg, 95%, GS 224342) as a white solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.83 (d, J = 6.9 Hz, 2H), 7.65-7.58 (m, 3H), 7.18 (d, J = 7.8 Hz, 2H), 6.90 (d, J = 7.8 Hz, 2H), 5.59

(d,  $J = 4.8$  Hz, 1H), 5.0 (m, 1H), 4.27 (d,  $J = 10.2$  Hz, 2H), 3.95-3.68 (m, 6H), 3.45 (dd, 1H), 3.18-2.84 (m, 6H), 2.50 (m, 1H), 2.02 (m, 1H), 1.6-1.38 (m, 5H), 0.93 (d,  $J = 6.3$  Hz, 3H), 0.88 (d,  $J = 6.3$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CD}_3\text{OD}$ ),  $\delta$  18.0.

#### 5 Example 46

Monophospholactate 51: A solution of 48 (0.28 g, 0.33 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.6 mL) at  $0^\circ\text{C}$  was treated with trifluoroacetic acid (0.3 mL). The solution was stirred for 30 min at  $0^\circ\text{C}$  and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in  $\text{CH}_2\text{Cl}_2$  (2 mL) and cooled to  $0^\circ\text{C}$ . Triethylamine (0.18 mL, 1.32 mmol) was added followed by the treatment of 4-fluorobenzenesulfonyl chloride (64 mg, 0.33 mmol). The solution was stirred at  $0^\circ\text{C}$  for 30 min and then warmed to room temperature for 30 min. The product was partitioned between  $\text{CH}_2\text{Cl}_2$  and 0.1 N HCl. The organic phase was washed with saturated NaCl, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the monophospholactate (0.16 g, 52%) as a white solid.

#### Example 47

20 Metabolite X 52: To a solution of 51 (80 mg, 0.09 mmol) in EtOH (6 mL) and EtOAc (2 mL) was added 10% Pd/C (20 mg). The suspension was stirred under  $\text{H}_2$  atmosphere (balloon) at room temperature for 8 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated, co-evaporated with  $\text{CHCl}_3$  and dried under vacuum to give the metabolite X (61 mg, 95%, GS 224343) as a white solid:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.9 (dd, 2H), 7.32 (m, 2H), 7.18 (dd, 2H), 6.90 (dd, 2H), 5.59 (d,  $J = 5.4$  Hz, 1H), 5.0 (m, 1H), 4.28 (d,  $J = 10.2$  Hz, 2H), 3.95-3.72 (m, 6H), 3.44 (dd, 1H), 3.15-2.85 (m, 6H), 2.5 (m, 1H), 2.02 (m, 1H), 1.55-1.38 (m, 5H), 0.93 (d,  $J = 6.3$  Hz, 3H), 0.88 (d,  $J = 6.3$  Hz, 3H).  $^{31}\text{P}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  18.2.

#### 30 Example 48

Monophospholactate 53: A solution of 48 (0.20 g, 0.24 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.6 mL) at  $0^\circ\text{C}$  was treated with trifluoroacetic acid (0.3 mL). The solution was stirred for 30 min at  $0^\circ\text{C}$  and



then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in  $\text{CH}_2\text{Cl}_2$  (2 mL) and cooled to  $0^\circ\text{C}$ . Triethylamine (0.16 mL, 1.20 mmol) was added followed by the treatment of hydrogen chloride salt of 3-pyridinysulfonyl chloride (50 mg, 0.24 mmol). The solution was stirred at  $0^\circ\text{C}$  for 30 min and then warmed to room temperature for 30 min. The product was partitioned between  $\text{CH}_2\text{Cl}_2$  and  $\text{H}_2\text{O}$ . The organic phase was washed with saturated NaCl, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude product was purified by column chromatography on silica gel (4% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the monophospholactate (0.11 g, 53%) as a white solid.

#### Example 49

Metabolite X 54: To a solution of 53 (70 mg, 0.09 mmol) in EtOH (5 mL) was added 10% Pd/C (20 mg). The suspension was stirred under  $\text{H}_2$  atmosphere (balloon) at room temperature for 5 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated, co-evaporated with  $\text{CHCl}_3$  and dried under vacuum to give the metabolite X (53 mg, 95%, GS 273834) as a white solid:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  8.99 (s, 1H), 8.79 (d,  $J$  = 4.2 Hz, 1H), 8.29 (d,  $J$  = 7.5 Hz, 1H), 7.7 (m, 1H), 7.15 (d,  $J$  = 8.4 Hz, 2H), 6.9 (d,  $J$  = 7.8 Hz, 2H), 5.59 (d,  $J$  = 5.4 Hz, 1H), 5.0 (m, 1H), 4.28 (d,  $J$  = 9.9 Hz, 2H), 3.97-3.70 (m, 6H), 3.44 (dd, 1H), 3.17-2.85 (m, 6H), 2.5 (m, 1H), 2.03 (m, 1H), 1.65-1.38 (m, 5H), 0.93 (d,  $J$  = 6.3 Hz, 3H), 0.88 (d,  $J$  = 6.3 Hz, 3H).  $^{31}\text{P}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  17.8.

#### Example 50

Monophospholactate 55: A solution of 48 (0.15 g, 0.18 mmol) in  $\text{CH}_2\text{Cl}_2$  (1 mL) at  $0^\circ\text{C}$  was treated with trifluoroacetic acid (0.5 mL). The solution was stirred for 30 min at  $0^\circ\text{C}$  and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in  $\text{CH}_2\text{Cl}_2$  (2 mL) and cooled to  $0^\circ\text{C}$ . Triethylamine (0.12 mL, 0.88 mmol) was added followed by the treatment of 4-benzyloxybenzenesulfonyl chloride (50 mg, 0.18 mmol). The solution was stirred at  $0^\circ\text{C}$  for 30 min and then warmed to room temperature for 30 min. The product was partitioned between  $\text{CH}_2\text{Cl}_2$  and 0.1 N HCl. The organic phase was washed with saturated NaCl, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and

concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the monophospholactate (0.11 g, 63%) as a white solid.

#### Example 51

- 5 Metabolite X 56: To a solution of 55 (70 mg, 0.07 mmol) in EtOH (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H<sub>2</sub> atmosphere (balloon) at room temperature for 4 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated, co-evaporated with CHCl<sub>3</sub> and dried under vacuum to give the metabolite X (46 mg, 90%, GS 273847) as a white solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD), δ 7.91 (s, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 6.91 (m, 4H), 5.59 (d, J = 5.1 Hz, 1H), 5.0 (m, 1H), 4.27 (d, J = 10.2 Hz, 2H), 3.97-3.74 (m, 6H), 3.4 (dd, 1H), 3.17-2.8 (m, 6H), 2.5 (m, 1H), 2.0 (m, 1H), 1.6-1.38 (m, 5H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); <sup>31</sup>P NMR (CD<sub>3</sub>OD) δ 17.9.

#### 15 Example 52

- Metabolite X 57: To a suspension of 29 (40 mg, 0.05 mmol) in CH<sub>3</sub>CN (1 mL), DMSO (0.5 mL), and 1.0 M PBS buffer (5 mL) was added esterase (200 µL). The suspension was heated to 40°C for 48 h. The reaction mixture was concentrated, suspended in MeOH and filtered. The filtrate was concentrated and purified by HPLC to give the metabolite X (20 mg, 57%, GS 277777) as a white solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 8.68 (s, 1H), 8.47 (d, J = 6.0 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.68 (m, 1H), 7.15 (d, J = 8.4 Hz, 2H), 6.9 (d, J = 8.4 Hz, 2H), 5.59 (d, J = 5.4 Hz, 1H), 5.0 (m, 1H), 4.23 (d, J = 10.5 Hz, 2H), 3.97-3.68 (m, 6H), 3.45 (dd, 1H), 3.15-2.87 (m, 6H), 2.46 (m, 1H), 2.0 (m, 1H), 1.6-1.38 (m, 5H), 0.95 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H); <sup>31</sup>P NMR (CD<sub>3</sub>OD) δ 17.2.

25

#### Example 53

- Metabolite X 58: To a suspension of 35 (60 mg, 0.07 mmol) in CH<sub>3</sub>CN (1 mL), DMSO (0.5 mL), and 1.0 M PBS buffer (5 mL) was added esterase (400 µL). The suspension was heated to 40°C for 3 days. The reaction mixture was concentrated, suspended in MeOH and filtered.
- 30 The filtrate was concentrated and purified by HPLC to give the metabolite X (20 mg, 38%, GS 278116) as a white solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.74 (d, J = 6.9 Hz, 2H), 7.63 (d, J = 7.5 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.1 Hz, 2H), 5.64 (d, J = 5.1 Hz, 1H), 5.0 (m,

2H), 4.41 (m, 2H), 4.22 (m, 2H), 3.97-3.65 (m, 12H), 3.15-2.9 (m, 8H), 2.75 (m, 1H), 2.0 (m, 1H), 1.8 (m, 2H), 1.53 (d, J = 6.9 Hz, 3H), 0.88 (m, 6H).

#### Example 54

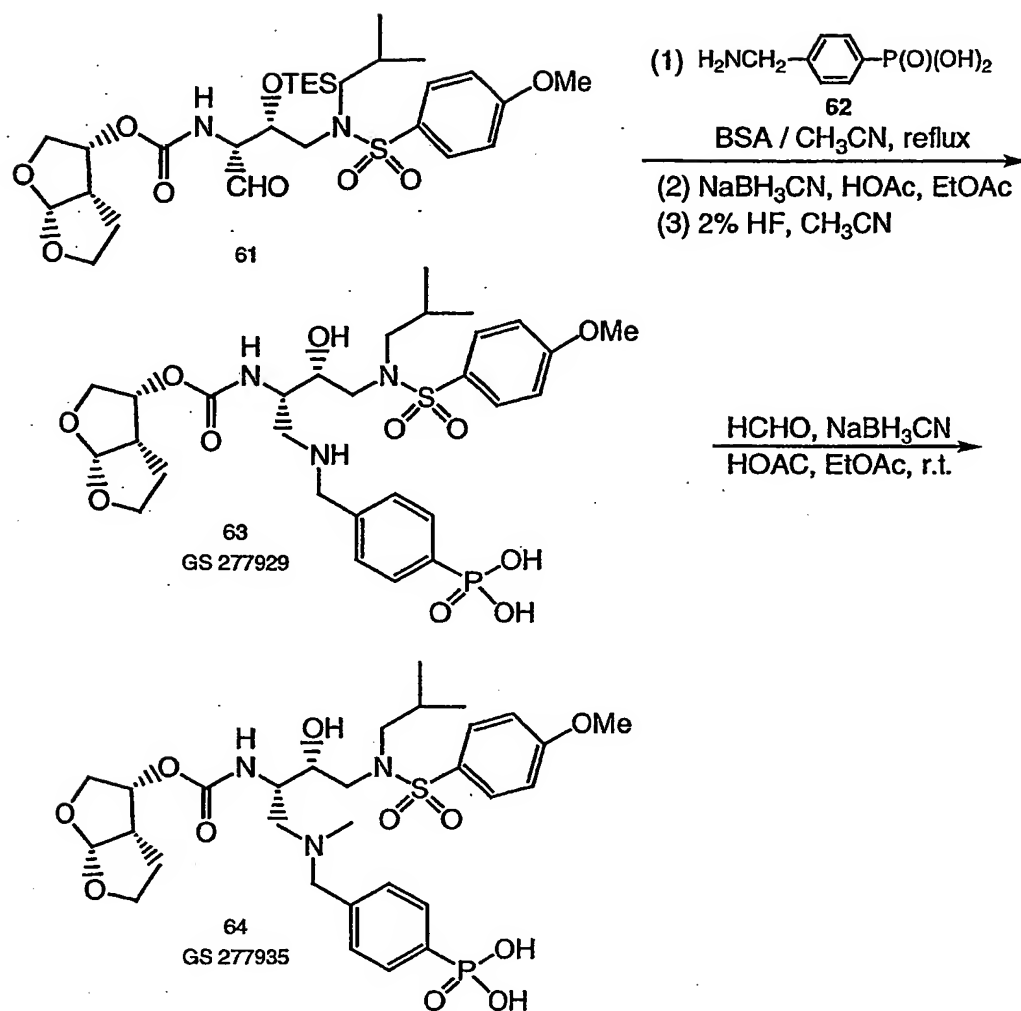
- 5 Monophospholactate 59: A solution of 34 (2.10 g, 2.48 mmol) in THF (72 mL) and H<sub>2</sub>O (8 mL) at -15°C was treated with NaBH<sub>4</sub> (0.24 g, 6.20 mmol). The reaction mixture was stirred for 10 min at -15°C. The reaction was quenched with 5% aqueous NaHSO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x). The combined organic layers were washed with H<sub>2</sub>O, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography on
- 10 silica gel (5% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give monophospholactate (1.89 g, 90%, GS 278053, 1:1 diastereomeric mixture) as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.64 (m, 2H), 7.51 (m, 2H), 7.38-7.19 (m, 7H), 6.92 (m, 2H), 5.69 (d, J = 4.8 Hz, 1H), 5.15 (m, 2H), 4.76 (s, 2H), 4.54 (d, J = 10.5 Hz, 1H), 4.44 (m, 1H), 4.2 (m, 2H), 4.04-3.68 (m, 6H), 3.06-2.62 (m, 7H), 1.8 (m, 3H), 1.62-1.5 (dd, 3H), 1.25 (m, 3H), 0.94 (d, J = 6.3 Hz, 3H), 0.87 (d, J = 6.3 Hz, 3H); <sup>31</sup>P
- 15 NMR (CDCl<sub>3</sub>) δ 17.4, 15.4.

#### Example 55

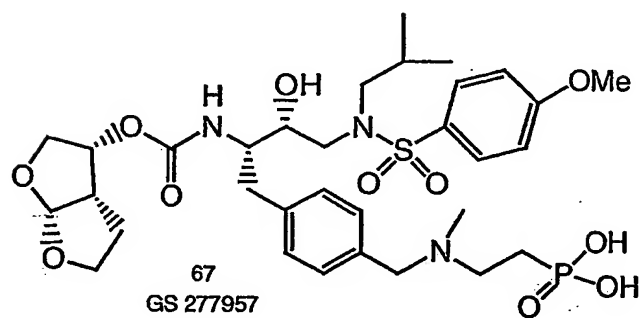
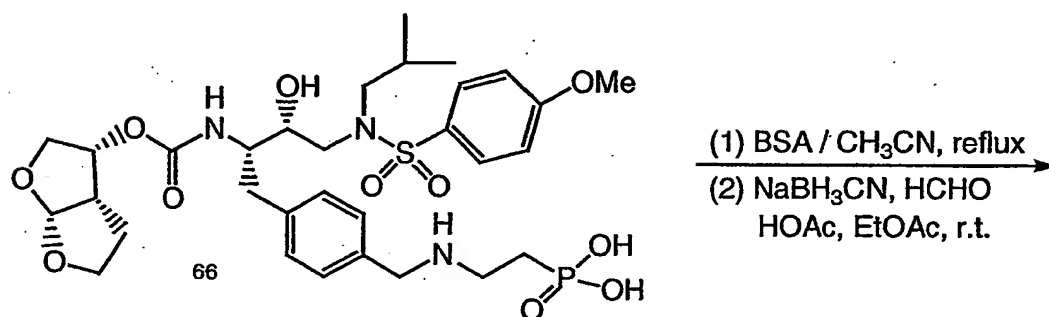
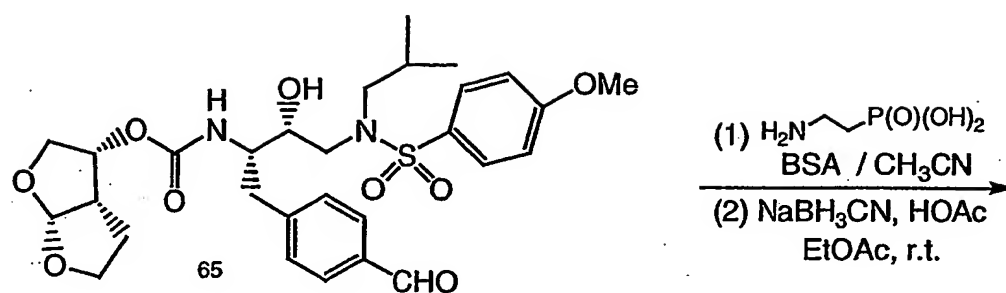
- Metabolite X 60: To a suspension of 59 (70 mg, 0.08 mmol) in CH<sub>3</sub>CN (1 mL), DMSO (0.5 mL), and 1.0 M PBS buffer (5 mL) was added esterase (600 μL). The suspension was heated
- 20 to 40°C for 36 h. The reaction mixture was concentrated, suspended in MeOH and filtered. The filtrate was concentrated and purified by HPLC to give the metabolite X (22 mg, 36%, GS 278764) as a white solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.78 (dd, 2H), 7.54 (dd, 2H), 7.15 (m, 2H), 6.9 (m, 2H), 5.57 (d, 1H), 5.0 (m, 2H), 4.65 (m, 4H), 4.2 (m, 2H), 3.9-3.53 (m, 6H), 3.06-2.82 (m, 6H), 2.5 (m, 1H), 2.0 (m, 2H), 1.62-1.35 (m, 3H), 0.94 (m, 6H).

25

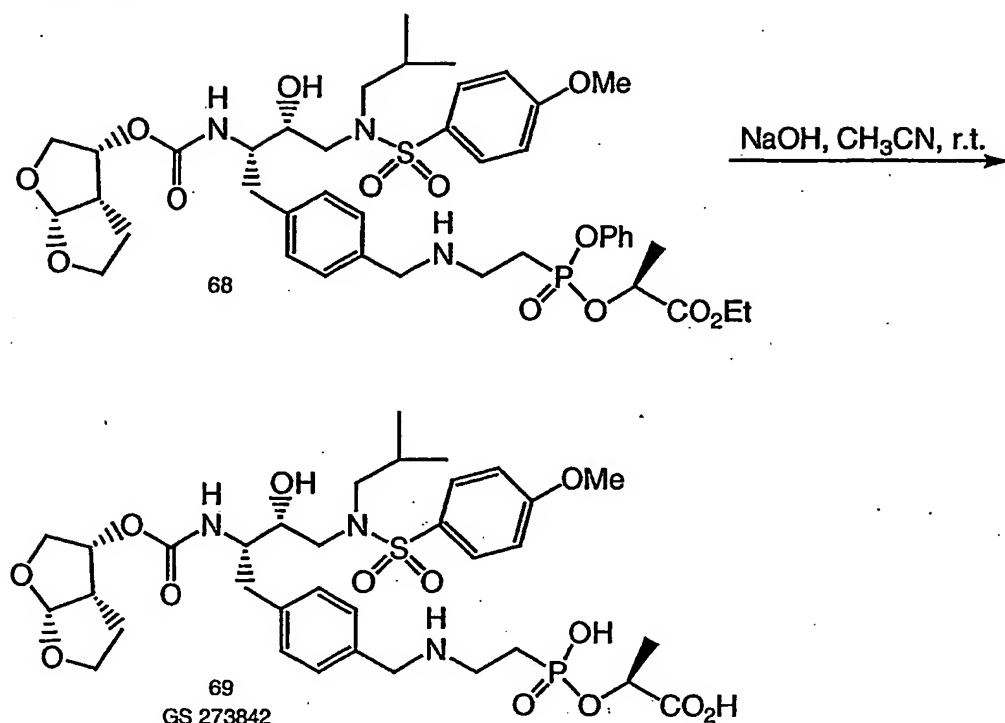
## Scheme 16



## Scheme 17



## Scheme 18



## Example 56

- 5 Phosphonic Acid 63: Compound 62 (0.30 g, 1.12 mmol) was dissolved in CH<sub>3</sub>CN (5 mL). *N,O*-Bis(trimethylsilyl)acetamide (BSA, 2.2 mL, 8.96 mmol) was added. The reaction mixture was heated to reflux for 2 h, cooled to room temperature, and concentrated. The residue was co-evaporated with toluene and chloroform and dried under vacuum to give a thick oil which was dissolved in EtOAc (4 mL) and cooled to 0°C. Aldehyde 61 (0.20 g, 0.33
- 10 mmol), AcOH (0.18 mL, 3.30 mmol), and NaBH<sub>3</sub>CN (0.20 g, 3.30 mmol) were added. The reaction mixture was warmed to room temperature and stirred overnight. The reaction was quenched with H<sub>2</sub>O, stirred for 30 min, filtered, and concentrated. The crude product was dissolved in CH<sub>3</sub>CN (13 mL) and 48% aqueous HF (0.5 mL) was added. The reaction mixture was stirred at room temperature for 2 h and concentrated. The crude product was
- 15 purified by HPLC to give the phosphonic acid (70 mg, 32%, GS 277929) as a white solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.92 (dd, 2H), 7.73 (d, J = 8.7 Hz, 2H), 7.63 (dd, 2H), 7.12 (d, J = 8.7 Hz, 2H), 5.68 (d, J = 5.1 Hz, 1H), 5.13 (m, 1H), 4.4 (m, 2H), 4.05-3.89 (m, 8H), 3.75 (m, 1H), 3.5 (m, 1H), 3.37 (m, 1H), 3.23-3.0 (m, 3H), 2.88-2.7 (m, 2H), 2.2 (m, 1H), 1.8 (m, 2H), 0.92 (d, J = 6.3 Hz, 3H), 0.85 (d, J = 6.3 Hz, 3H); <sup>31</sup>P NMR (CD<sub>3</sub>OD) δ 14.5.

Example 57

Phosphonic Acid 64: A solution of 63 (50 mg, 0.07 mmol) and formaldehyde (60 mg, 0.70 mmol) in EtOAc (2 mL) was treated with HOAc (43  $\mu$ L, 0.70 mmol) and NaBH<sub>3</sub>CN (47 mg, 0.7 mmol). The reaction mixture was stirred at room temperature for 26 h. The reaction was quenched with H<sub>2</sub>O, stirred for 20 min, and concentrated. The crude product was purified by HPLC to give the phosphonic acid (15 mg, 29%, GS 277935) as a white solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  7.93 (m, 2H), 7.75 (m, 2H), 7.62 (m, 2H), 7.11 (m, 2H), 5.66 (m, 1H), 5.13 (m, 1H), 4.4 (m, 2H), 4.05-3.89 (m, 8H), 3.75 (m, 2H), 3.09-2.71 (m, 6H), 2.2 (m, 1H), 1.9 (m, 5H), 0.92 (d, J = 6.3 Hz, 3H), 0.85 (d, J = 6.3 Hz, 3H); <sup>31</sup>P NMR (CD<sub>3</sub>OD)  $\delta$  14.0.

Example 58

Phosphonic Acid 66: 2-Aminoethylphosphonic acid (2.60 g, 21.66 mmol) was dissolved in CH<sub>3</sub>CN (40 mL). *N,O*-Bis(trimethylsilyl)acetamide (BSA, 40 mL) was added. The reaction mixture was heated to reflux for 2 h and cooled to room temperature and concentrated. The residue was co-evaporated with toluene and chloroform and dried under vacuum to give a thick oil which was dissolved in EtOAc (40 mL). Aldehyde 65 (1.33 g, 2.25 mmol), AcOH (1.30 mL, 22.5 mmol) and NaBH<sub>3</sub>CN (1.42 g, 22.5 mmol) were added. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with H<sub>2</sub>O, stirred for 1 h, filtered, and concentrated. The residue was dissolved in MeOH and filtered. The crude product was purified by HPLC to give the phosphonic acid (1.00 g, 63%) as a white solid.

Example 59

Phosphonic Acid 67: Phosphonic acid 66 (0.13 g, 0.19 mmol) was dissolved in CH<sub>3</sub>CN (4 mL). *N,O*-Bis(trimethylsilyl)acetamide (BSA, 0.45 mL, 1.90 mmol) was added. The reaction mixture was heated to reflux for 2 h, cooled to room temperature, and concentrated. The residue was co-evaporated with toluene and chloroform and dried under vacuum to give a thick oil which was dissolved in EtOAc (3 mL). Formaldehyde (0.15 mL, 1.90 mmol), AcOH (0.11 mL, 1.90 mmol) and NaBH<sub>3</sub>CN (63 mg, 1.90 mmol) were added. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with H<sub>2</sub>O, stirred for 6 h, filtered, and concentrated. The residue was dissolved in MeOH and filtered. The crude product was purified by HPLC to give the phosphonic acid (40 mg, 30%, GS

277957) as a white solid:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.78 (d,  $J = 8.4$  Hz, 2H), 7.4 (m, 4H), 7.09 (d,  $J = 8.4$  Hz, 2H), 5.6 (d,  $J = 5.1$  Hz, 1H), 4.33 (m, 2H), 3.95-3.65 (m, 9H), 3.5-3.05 (m, 6H), 2.91-2.6 (m, 7H), 2.0 (m, 3H), 1.5 (m, 2H), 0.93 (d,  $J = 6.3$  Hz, 3H), 0.87 (d,  $J = 6.3$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  19.7.

5

### Example 60

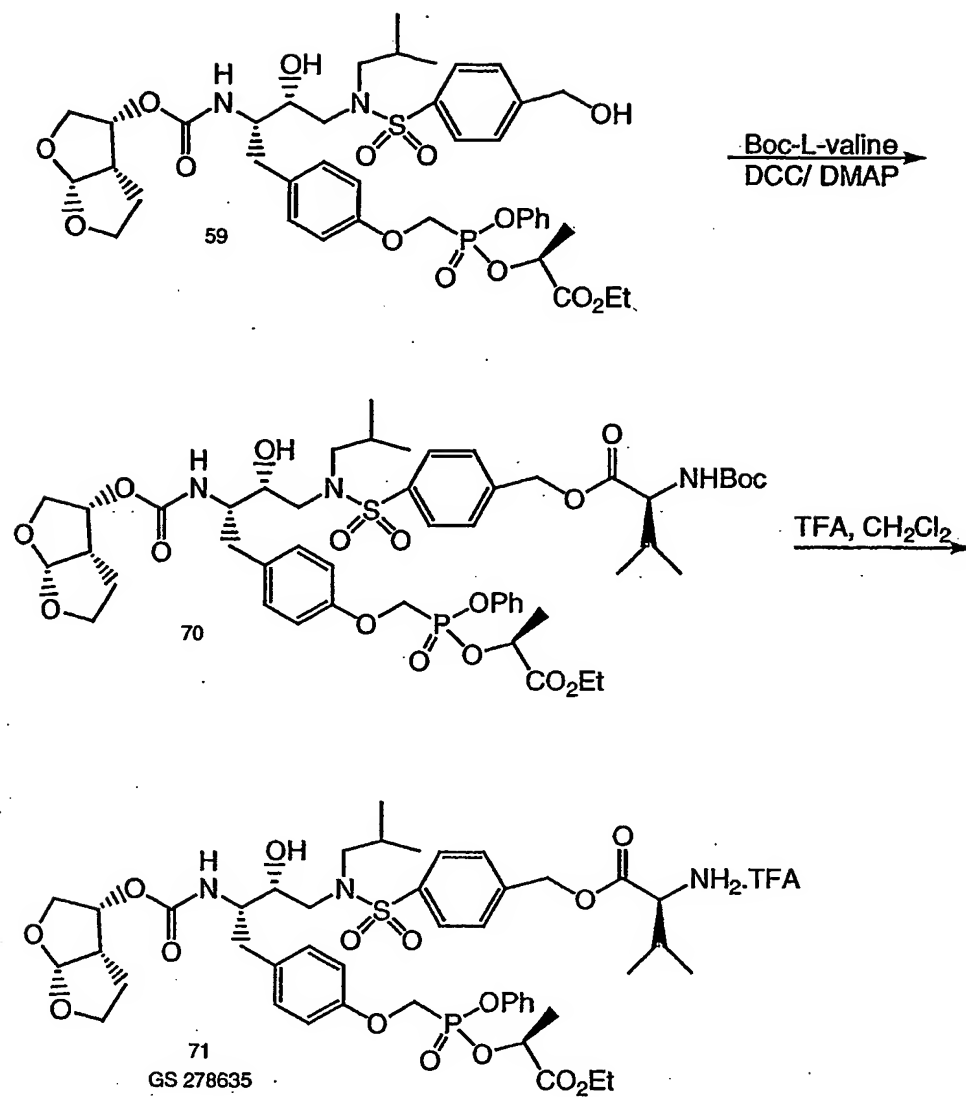
Metabolite X 69: Monophospholactate 68 (1.4 g, 1.60 mmol) was dissolved in  $\text{CH}_3\text{CN}$  (20 mL) and  $\text{H}_2\text{O}$  (20 mL). 1.0 N NaOH (3.20 mL, 3.20 mmol) was added. The reaction mixture was stirred at room temperature for 1.5 h and cooled to  $0^\circ\text{C}$ . The reaction mixture was acidified to pH = 1-2 with 2 N HCl (1.6 mL, 3.20 mmol). The solvent was evaporated under reduced pressure. The crude product was purified by HPLC to give the metabolite X (0.60 g, 49%, GS 273842) as a white solid:  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  7.72 (d,  $J = 8.7$  Hz, 2H), 7.33 (m, 4H), 7.09 (d,  $J = 9.0$  Hz, 2H), 5.52 (d,  $J = 5.7$  Hz, 1H), 5.1 (broad s, 1H), 4.85 (m, 1H), 4.63 (m, 1H), 4.13 (m, 2H), 3.8 (m, 5H), 3.6 (m, 4H), 3.36 (m, 1H), 3.03 (m, 4H), 2.79 (m, 3H), 2.5 (m, 1H), 2.0 (m, 3H), 1.5-1.3 (m, 5H), 0.85 (d,  $J = 6.6$  Hz, 3H), 0.79 (d,  $J = 6.6$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  21.9.

10

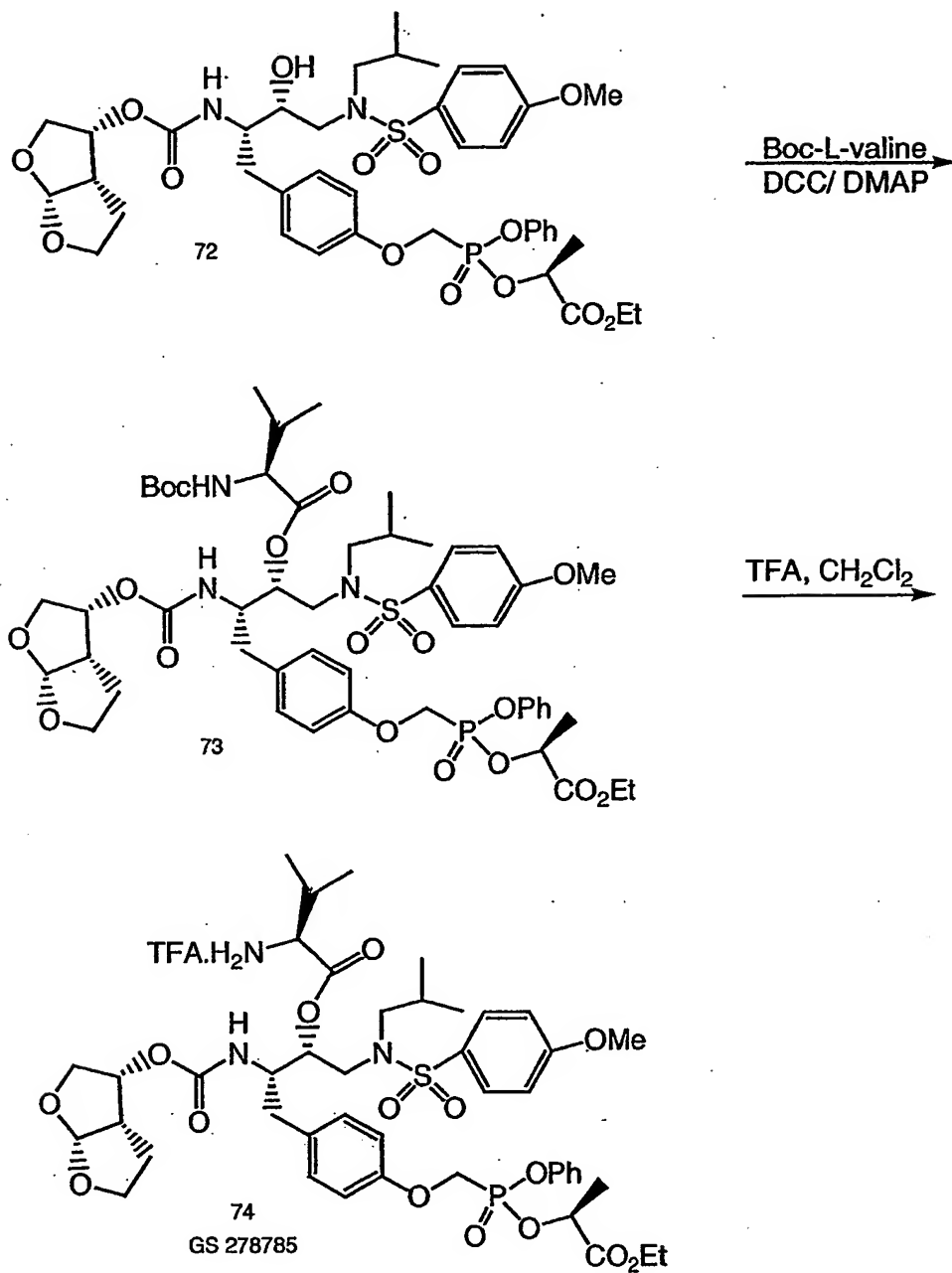
15



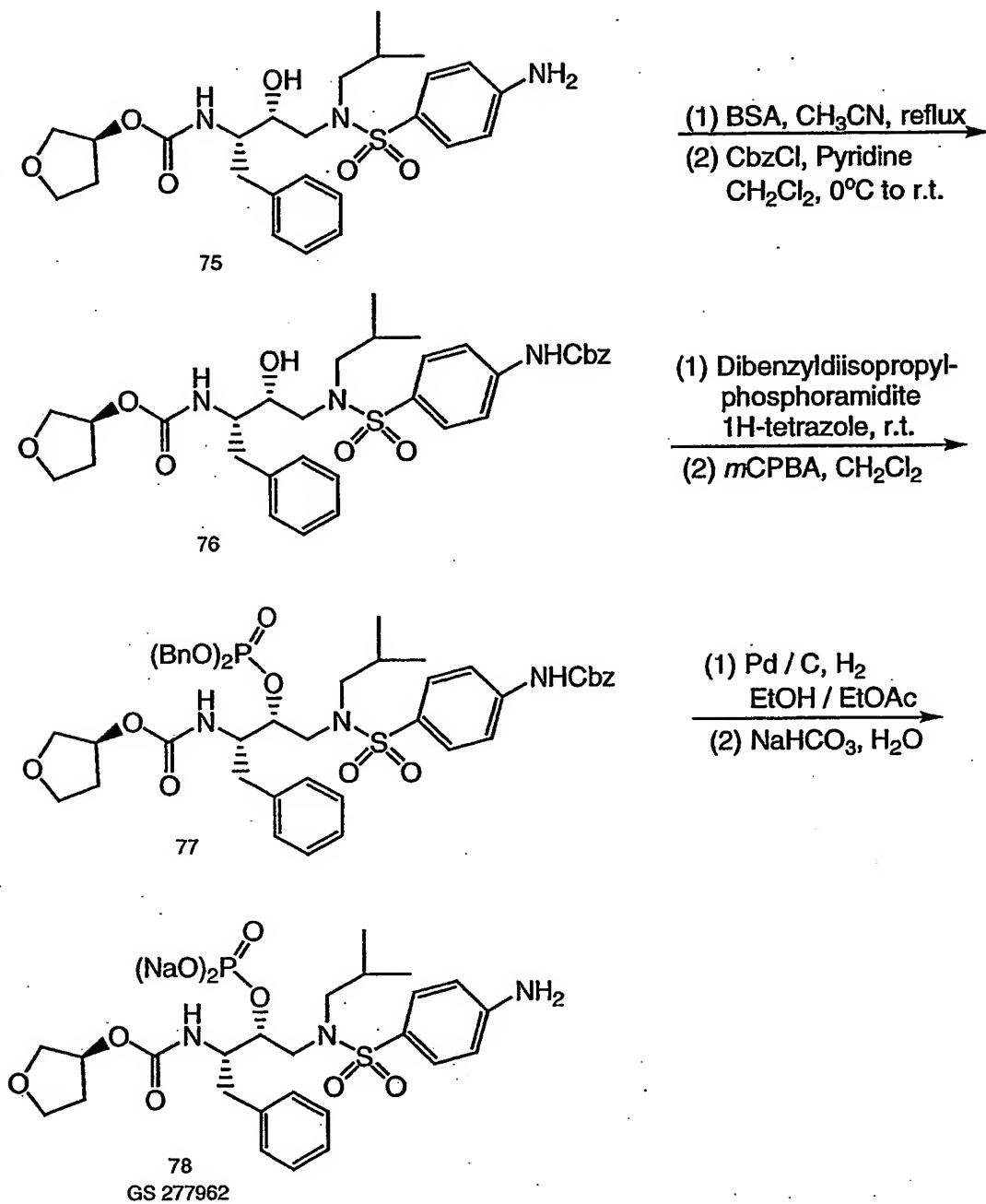
## Scheme 19



Scheme 20



## Scheme 21

5 Example 61

**Monophospholactate 70:** A solution of 59 (1.48 g, 1.74 mmol) and Boc-L-valine (0.38 g, 1.74 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) at 0°C was treated with 1,3-dicyclohexylcarbodiimide (0.45 g, 2.18 mmol) and 4-dimethylaminopyridine (26 mg, 0.21 mmol). The reaction mixture was stirred at 0°C for 1 h and then warmed to room temperature for 2 h. The product was

partitioned between  $\text{CH}_2\text{Cl}_2$  and 0.2 N HCl. The organic layer was washed with  $\text{H}_2\text{O}$ , dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude product was purified by column chromatography on silica gel (4% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the monophospholactate (1.65 g, 90%) as a white solid.

5

#### Example 62

Monophospholactate 71: A solution of 70 (1.65 g, 1.57 mmol) in  $\text{CH}_2\text{Cl}_2$  (8 mL) at  $0^\circ\text{C}$  was treated with trifluoroacetic acid (4 mL). The solution was stirred for 30 min at  $0^\circ\text{C}$  and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with  
10 toluene and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (10% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the monophospholactate (1.42 g, 85%, GS 278635, 2/3 diastereomeric mixture) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.73 (m, 2H), 7.49 (d,  $J = 7.2$  Hz, 2H), 7.4-7.1 (m, 7H), 6.89 (m, 2H), 5.64 (m, 1H), 5.47 (m, 1H), 5.33-5.06 (m, 4H), 4.57-4.41 (m, 2H), 4.2 (m, 2H), 3.96-3.7 (m, 7H), 3.15-2.73 (m, 7H),  
15 2.38 (m, 1H), 1.9 (m, 1H), 1.7 (m, 1H), 1.63-1.5 (m, 4H), 1.24 (m, 3H), 1.19 (m, 6H), 0.91 (d, 3H), 0.88 (d, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.3, 15.4.

#### Example 63

Monophospholactate 73: A solution of 72 (0.43 g, 0.50 mmol) and Boc-L-valine (0.11 g, 0.50 mmol) in  $\text{CH}_2\text{Cl}_2$  (6 mL) was treated with 1,3-dicyclohexylcarbodiimide (0.13 g, 0.63  
20 mmol) and 4-dimethylaminopyridine (62 mg, 0.5 mmol). The reaction mixture was stirred at room temperature overnight. The product was partitioned between  $\text{CH}_2\text{Cl}_2$  and 0.2 N HCl. The organic layer was washed with  $\text{H}_2\text{O}$ , dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude product was purified by column chromatography on silica gel (2% 2-propanol/ $\text{CH}_2\text{Cl}_2$ )  
25 to give the monophospholactate (0.45 g, 85%) as a white solid.

#### Example 64

Monophospholactate 74: A solution of 73 (0.44 g, 0.42 mmol) in  $\text{CH}_2\text{Cl}_2$  (1 mL) at  $0^\circ\text{C}$  was treated with trifluoroacetic acid (0.5 mL). The solution was stirred for 30 min at  $0^\circ\text{C}$  and  
30 then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (10% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the monophospholactate (0.40 g, 90%, GS 278785, 1:1 diastereomeric mixture) as a white solid:

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.69 (d, J = 8.4 Hz, 2H), 7.34-7.2 (m, 7H), 6.98 (d, J = 8.4 Hz, 2H), 6.88 (m, 2H), 6.16 (m, 1H), 5.64 (m, 1H), 5.46 (m, 1H), 5.2-5.0 (m, 2H), 4.5 (m, 2H), 4.2 (m, 3H), 4.0-3.4 (m, 9H), 3.3 (m, 1H), 3.0-2.8 (m, 5H), 2.5 (m, 1H), 1.83 (m, 1H), 1.6-1.5 (m, 5H), 1.25 (m, 3H), 1.15 (m, 6H), 0.82 (d, J = 6.0 Hz, 3H), 0.76 (d, J = 6.0 Hz, 3H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 17.3, 15.5.

#### Example 65

Cbz Amide 76: Compound 75 (0.35 g, 0.69 mmol) was dissolved in CH<sub>3</sub>CN (6 mL). *N,O*-Bis(trimethylsilyl)acetamide (BSA, 0.67 mL, 2.76 mmol) was added. The reaction mixture was heated to reflux for 1 h, cooled to room temperature, and concentrated. The residue was co-evaporated with toluene and chloroform and dried under vacuum to give a thick oil which was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) and cooled to 0°C. Pyridine (0.17 mL, 2.07 mmol) and benzyl chloroformate (0.12 mL, 0.83 mmol) were added. The reaction mixture was stirred at 0°C for 1 h and then warmed to room temperature overnight. The reaction was quenched with MeOH (5 mL) and 10% HCl (20 mL) at 0°C and stirred for 1 h. The product was extracted with CH<sub>2</sub>Cl<sub>2</sub>, washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the CBz amide (0.40 g, 90%) as a white solid.

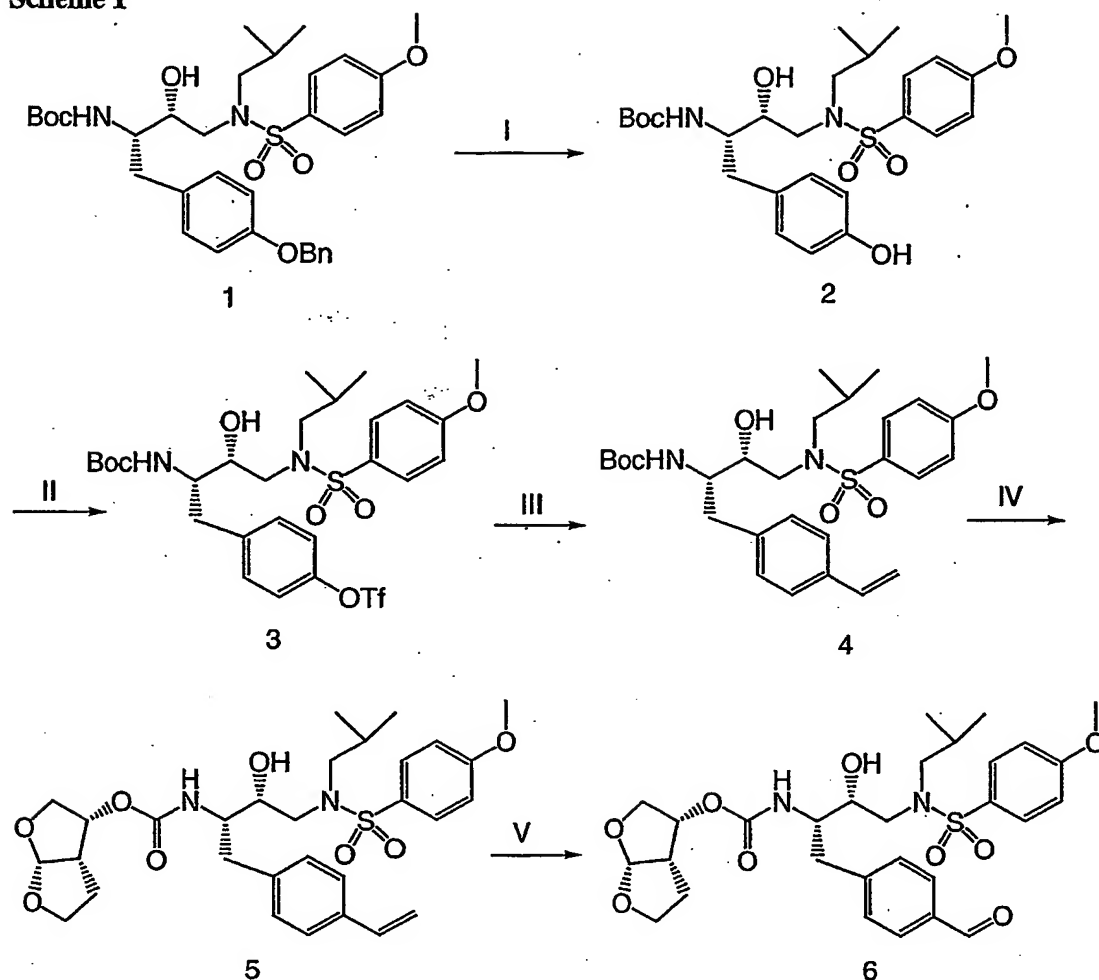
#### Example 66

Dibenzylphosphonate 77: A solution of 76 (0.39 g, 0.61 mmol) and 1*H*-tetrazole (54 mg, 0.92 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (8 mL) was treated with dibenzyl-diisopropylphosphoramidite (0.32 g, 0.92 mmol) and stirred at room temperature overnight. The solution was cooled to 0°C, treated with *m*CPBA, stirred for 1 h at 0°C and then warmed to room temperature for 1 h. The reaction mixture was poured into a mixture of aqueous Na<sub>2</sub>SO<sub>3</sub> and NaHCO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with H<sub>2</sub>O, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the dibenzylphosphonate (0.42 g, 76%) as a white solid.

#### Example 67

Disodium Salt of Phosphonic Acid 78: To a solution of 77 (0.18 g, 0.20 mmol) in EtOH (20 mL) and EtOAc (4 mL) was added 10% Pd/C (40 mg). The suspension was stirred under H<sub>2</sub> atmosphere (balloon) at room temperature for 4 h. The reaction mixture was filtered through

a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (0.11 g, 95%) which was dissolved in H<sub>2</sub>O (4 mL) and treated with NaHCO<sub>3</sub> (32 mg, 0.38 mmol). The reaction mixture was stirred at room temperature for 1 h and lyophilized overnight to give the disodium salt of phosphonic acid (0.12 g, 99%, GS 5 277962) as a white solid: <sup>1</sup>H NMR (D<sub>2</sub>O) δ 7.55 (dd, 2H), 7.2 (m, 5H), 7.77 (dd, 2H), 4.65 (m, 1H), 4.24 (m, 1H), 4.07 (m, 1H), 3.78-2.6 (m, 12H), 1.88-1.6 (m, 3H), 0.75 (m, 6H).

**Scheme 1**

I.  $\text{H}_2/10\%\text{Pd-C}/\text{EtOAc-EtOH}$  ; II.  $\text{Tf}_2\text{NPh}/\text{Cs}_2\text{CO}_3$ ;  
 III.  $\text{Bu}_3\text{SnCH=CH}_2/\text{PdCl}_2(\text{PPh}_3)_2/\text{LiCl}/\text{DMF}/90^\circ\text{C}$ ;  
 IV.a.  $\text{TFA}/\text{CH}_2\text{Cl}_2$ ; b. Bisfuran carbonate/ $i\text{-Pr}_2\text{NEt}/\text{DMAP}$ ;  
 V.  $\text{NaIO}_4/\text{OsO}_4/\text{EtOAc-H}_2\text{O}$

**Example 1**

- 5 Compound 1 was prepared by methods from Examples herein.

**Example 2**

Compound 2: To a solution of compound 1 (47.3 g) in EtOH/EtOAc (1000 mL/500 mL) was added 10% Pd-C (5 g). The mixture was hydrogenated for 19 hours. Celite was added and

the mixture was stirred for 10 minutes. The mixture was filtered through a pad of celite and was washed with ethyl acetate. Concentration gave compound 2 (42.1 g).

### Example 3

5 Compound 3: To a solution of compound 2 (42.3 g, 81 mmol) in  $\text{CH}_2\text{Cl}_2$  (833 mL) was added N-phenyltrifluoromethanesulfonimide (31.8 g, 89 mmol), followed by cesium carbonate (28.9 g, 89 mmol). The mixture was stirred for 24 hours. The solvent was removed under reduced pressure, and ethyl acetate was added. The reaction mixture was washed with water (3x) and brine (1x), and was dried over  $\text{MgSO}_4$ . Purification by flash  
10 column chromatography ( $\text{CH}_2\text{Cl}_2/\text{EtOAc} = 13/1$ ) gave compound 3 (49.5 g) as a white powder.

### Example 4

Compound 4: To a solution of compound 3 (25.2, 38.5 mmol) in DMF (240 mL) was added  
15 lithium chloride (11.45 g, 270 mmol), followed by dichlorobis(triphenylphosphine) palladium(II) (540 mg, 0.77 mmol). The mixture was stirred for 3 minutes under high vacuum and recharged with nitrogen. To the above solution was added tributylvinyltin (11.25 mL). The reaction mixture was heated at  $90^\circ\text{C}$  for 6 hours and cooled to  $25^\circ\text{C}$ . Water was added to the reaction, and the mixture was extracted with ethyl acetate (3X). The  
20 combined organic layer was washed with water (6x) and brine, and dried over  $\text{MgSO}_4$ . Concentration gave an oil. The oil was diluted with dichloromethane (40 mL), water (0.693 mL, 38.5 mmol) and DBU (5.76 mL, 38.5 mmol) were added. The mixture was stirred for 5 minutes, and subjected to flash column chromatography (hexanes/ $\text{EtOAc} = 2.5/1$ ). Compound 4 was obtained as white solid (18.4 g).

25

### Example 5

Compound 5: To a solution of compound 4 (18.4 g, 34.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (70 mL) at  $0^\circ\text{C}$  was added trifluoroacetic acid (35 mL). The mixture was stirred at  $0^\circ\text{C}$  for 2 hrs, and solvents were evaporated under reduced pressure. The reaction mixture was quenched with  
30 saturated sodium carbonate solution, and was extracted with ethyl acetate (3x). The combined organic layer was washed with saturated sodium carbonate solution(1x), water (2x), and brine (1x), and dried over  $\text{MgSO}_4$ . Concentration gave a solid. To a solution of the above solid in acetonitrile (220 mL) at  $0^\circ\text{C}$  was added bisfurancarboxylate (10.09 g, 34.2

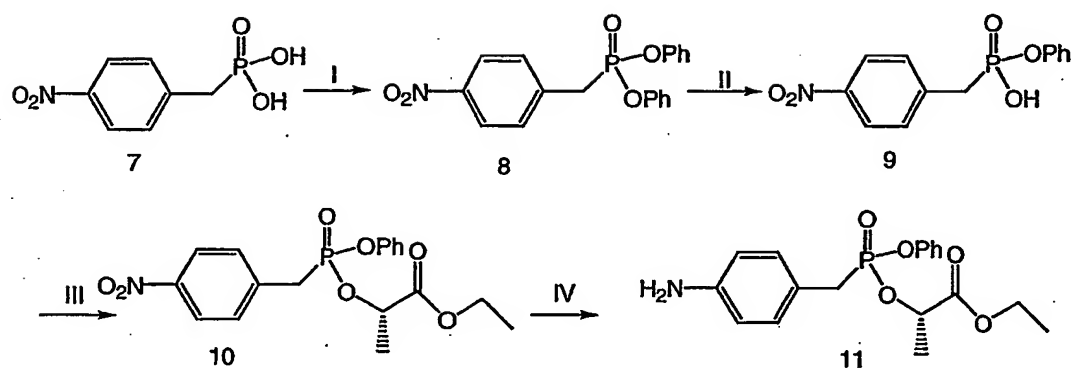


mmol), followed by di-isopropylethylamine (12.0 mL, 69.1 mmol) and DMAP (843 mg, 6.9 mmol). The mixture was warmed to 25°C and stirred for 12 hours. Solvents were removed under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with water (2X), 5% hydrochloric acid (2x), water (2x), 1N sodium hydroxide (2x), water (2x),  
5 and brine (1x), and dried over MgSO<sub>4</sub>. Purification by flash column chromatography (hexanes/EtOAc = 1/1)) gave compound 5 (13.5 g).

#### Example 6

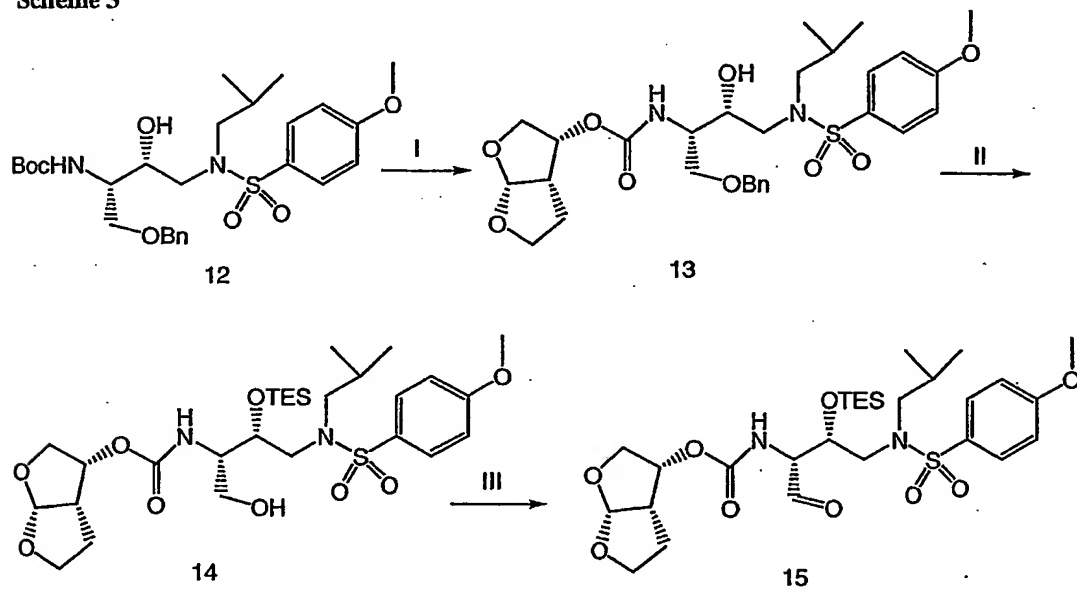
Compound 6: To a solution of compound 5 (13.5 g, 23 mmol) in ethyl acetate (135 mL) was  
10 added water (135 mL), followed by 2.5% osmium tetroxide/tert-butanol (17 mL). Sodium periodate (11.5 g) was added in portions over 2 minutes period. The mixture was stirred for 90 minutes, and was diluted with ethyl acetate. The organic layer was separated and washed with water (3x) and brine (1x), and dried over MgSO<sub>4</sub>. Purification by flash column chromatography (hexanes/EtOAc = 1/2) gave compound 6 as white powder (12 g): <sup>1</sup>H NMR  
15 (CDCl<sub>3</sub>) δ 9.98 (1 H, s), 7.82 (2 H, m), 7.75 (2 H, m), 7.43 (2 H, m), 6.99 (2 H, m), 5.64 (1 H, m), 5.02 (2 H, m), 4.0-3.8 (9 H, m), 3.2-2.7 (7 H, m), 1.9-1.4 (3 H, m), 0.94 (6 H, m).

Scheme 2



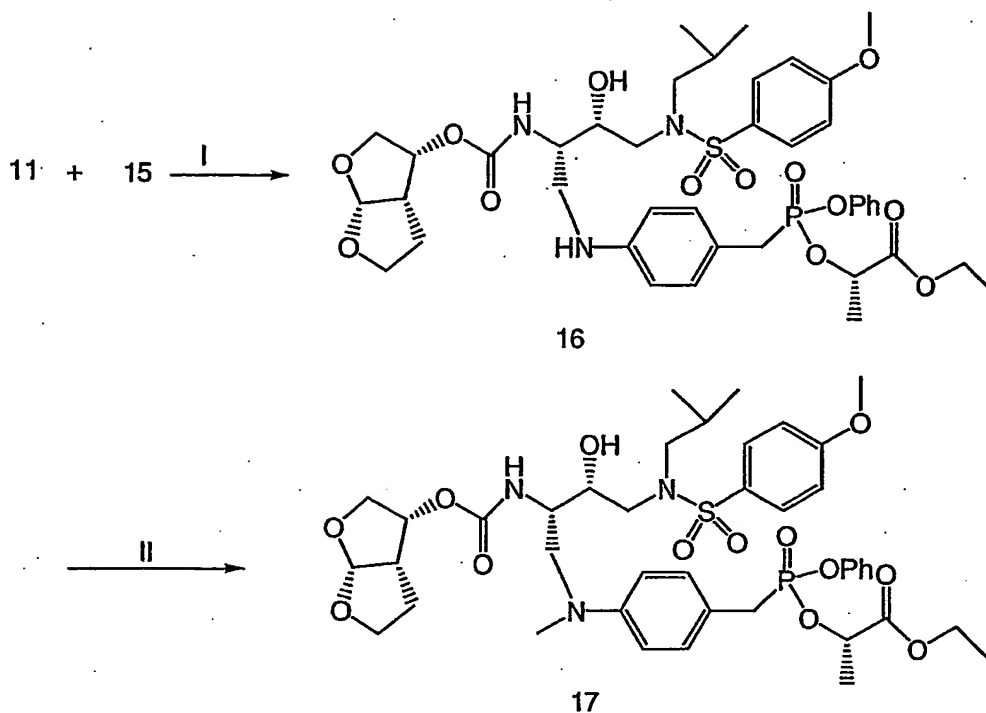
I. a.  $\text{SOCl}_2$ /toluene/60 C; b. PhOH/pyridine; II. a. NaOH/THF/ $\text{H}_2\text{O}$ ; b. HCl;  
 III. b.  $\text{SOCl}_2$ /toluene/60 C; c. ethyl lactate/pyridine; IV.  $\text{H}_2$ /10%Pd-C/EtOAc

Scheme 3



I. a. TFA/ $\text{CH}_2\text{Cl}_2$ ; b. bisfurancarboxylate/ $i\text{-Pr}_2\text{NEt}$ /DMAP; II. a.  $\text{Et}_3\text{SiCl}$ /imidazole/DMF;  
 b.  $\text{H}_2$ /20%Pd(OH) $_2$ -C/ $i\text{PrOH}$ ; III. Des-Martin reagent/ $\text{CH}_2\text{Cl}_2$

Scheme 4



I. a.  $\text{NaBH}_3\text{CN}/\text{HOAc}/\text{EtOAc}$ ; b.  $2\%\text{HF}/\text{CH}_3\text{CN}$ ;  
 II.  $\text{HCHO}/\text{NaBH}_3\text{CN}/\text{HOAc}/\text{EtOAc}$

Example 8

Compound 8: To the suspension of compound 7 (15.8 g, 72.5 mmol) in toluene (140 mL) was added DMF (1.9 mL), followed by thionyl chloride (53 mL, 725 mmol). The reaction mixture was heated at  $60^\circ\text{C}$  for 5 hrs, and evaporated under reduced pressure. The mixture was coevaporated with toluene (2x), EtOAc, and  $\text{CH}_2\text{Cl}_2$  (2x) to afford a brown solid. To the solution of the brown solid in  $\text{CH}_2\text{Cl}_2$  at  $0^\circ\text{C}$  was added phenol (27.2 g, 290 mmol), followed by slow addition of pyridine (35 mL, 435 mmol). The reaction mixture was allowed to warm to  $25^\circ\text{C}$  and stirred for 14 hrs. Solvents were removed under reduced pressure. The mixture was diluted with EtOAc, and washed with water (3x) and brine (1x), and dried over  $\text{MgSO}_4$ . Concentration gave a dark oil, which was purified by flash column chromatography (hexanes/EtOAc = 4/1 to 1/1) to afford compound 8 (12.5 g).

15 Example 9

Compound 9: To a solution of compound 8 (2.21 g, 6 mmol) in THF (30 mL) was added 12 mL of 1.0 N NaOH solution. The mixture was stirred at 25°C for 2 hours, and THF was removed under reduced pressure. The mixture was diluted with water, and acetic acid (343 mL, 6 mmol) was added. The aqueous phase was washed with EtOAc (3x), and then  
5 acidified with concentrated HCl until pH = 1. The aqueous was extracted with EtOAc (3x). The combined organic layer was washed with water (1x) and brine (1x), and dried over MgSO<sub>4</sub>. Concentration under reduced pressure gave compound 9 as a solid (1.1 g).

#### Example 10

10 Compound 10: To a suspension of compound 9 (380 mg, 1.3 mmol) in toluene (2.5 mL) was added thionyl chloride (1 mL, 13 mmol), followed by DMF (1 drop). The mixture was heated at 60°C for 2 hours. The solvent and reagent were removed under reduced pressure. The mixture was coevaporated with toluene (2x) and CH<sub>2</sub>Cl<sub>2</sub> to give a white solid. To the  
15 solution of the above solid in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) at -20°C was added ethyl lactate (294 µL, 2.6 mmol), followed by pyridine (420 µL, 5.2 mmol). The mixture was warmed to 25°C and stirred for 12 hours. The reaction mixture was concentrated under reduced pressure to give a yellow solid, which was purified by flash column chromatography to generate compound 10 (427 mg).

#### Example 11

20 Compound 11: To a solution of compound 10 (480 mg) in EtOAc (20 mL) was added 10% Pd-C (80 mg). The reaction mixture was hydrogenated for 6 hrs. The mixture was stirred with celite for 5 mins, and filtered through a pad of celite. Concentration under reduced  
25 pressure gave compound 11 (460 mg).

#### Example 12

Compound 12 was prepared by the methods of the Examples herein

#### Example 13

30 Compound 13: To a solution of compound 12 (536 mg, 1.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred for 2 hrs, and was concentrated under reduced pressure. The liquid was coevaporated with CH<sub>2</sub>Cl<sub>2</sub> (3x) and EtOAc (3x) to give a brown solid. To the solution of above brown solid in acetonitrile (6.5 mL) at 0°C was

added bisfurancarboxylate (295 mg, 1.0 mmol), followed by diisopropylethylamine (350  $\mu$ L, 2.0 mmol) and DMAP (24 mg). The mixture was warmed to 25°C, and was stirred for 12 hrs. The mixture was diluted with EtOAc, and was washed sequentially with water (2x), 0.5 N HCl (2x), water (2x), 0.5 N NaOH solution (2x), water (2x), and brine (1x), and dried over  
5 MgSO<sub>4</sub>. Purification by flash column chromatography (hexanes/EtOAc = 1/1) afford compound 13 (540 mg).

#### Example 14

Compound 14: To a solution of compound 13 (400 mg, 0.67 mmol) in DMF (3 mL) was  
10 added imidazole (143 mg, 2.10 mmol), followed by triethylchlorosilane (224  $\mu$ L, 1.34 mmol). The mixture was stirred for 12 hours. The mixture was diluted with EtOAc, and was washed with water (5x) and brine, and dried over MgSO<sub>4</sub>. Purification by flash column chromatography (hexanes/EtOAc = 2/1) gave a white solid (427 mg). To the solution of above solid in isopropanol (18 mL) was added 20% palladium(II) hydroxide on carbon (120  
15 mg). The mixture was hydrogenated for 12 hours. The mixture was stirred with celite for 5 mins, and filtered through a pad of celite. Concentration under reduced pressure gave compound 14(360 mg).

#### Example 15

20 Compound 15: To a solution of compound 14 (101 mg, 0.18 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added Dess-Martin periodiane (136 mg, 0.36 mmol). The mixture was stirred for 1 hour. Purification by flash column chromatography (hexanes/EtOAc = 2/1) gave compound 15 (98 mg).

#### Example 16

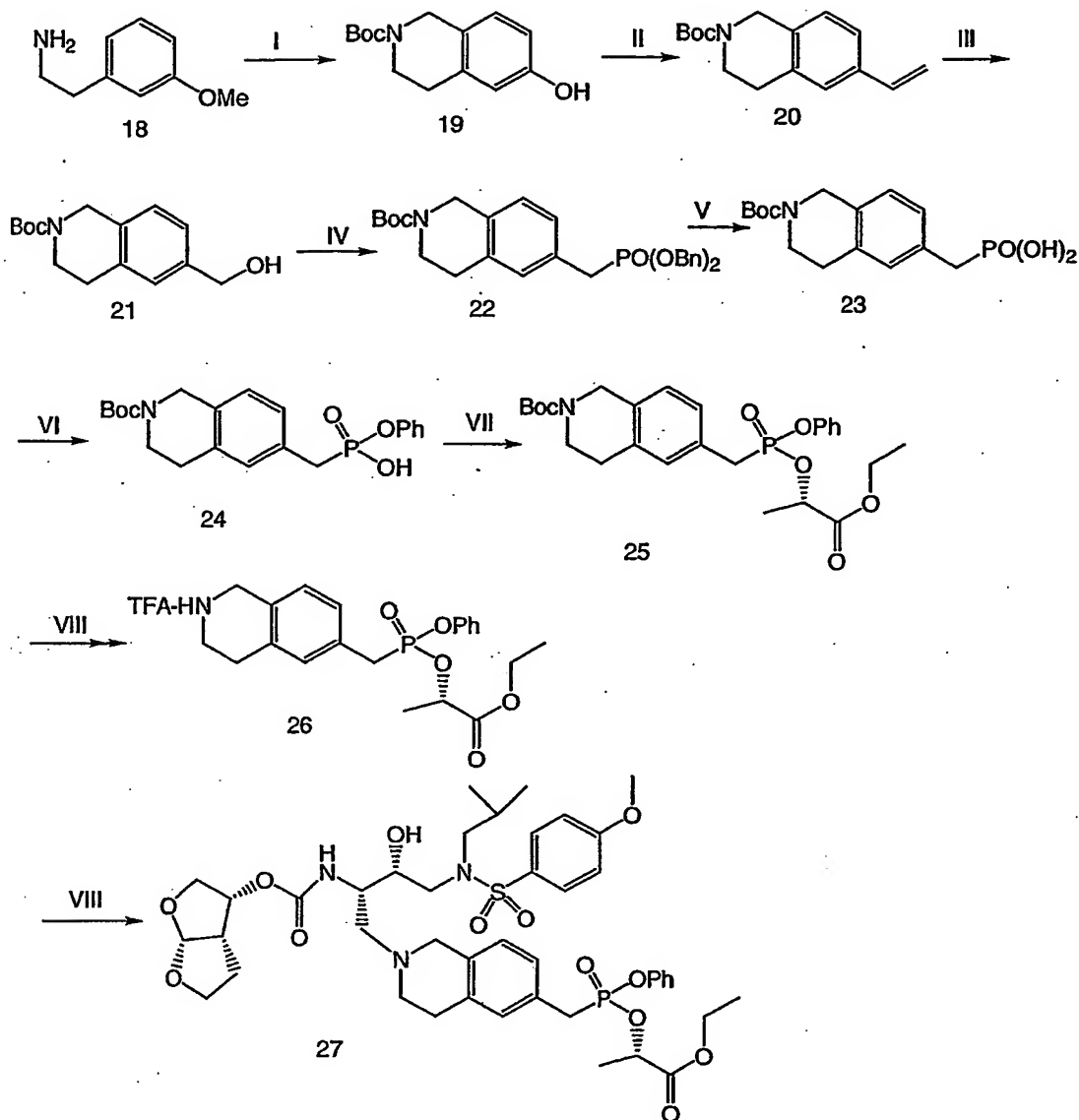
Compound 16: To a solution of compound 15 (50 mg, 0.08 mmol) in EtOAc (0.5 mL) was added compound 11 (150 mg, 0.41 mmol). The mixture was cooled to 0°C, acetic acid (19  $\mu$ L, 0.32 mmol) was added, followed by sodium cyanoborohydride (10 mg, 0.16 mmol). The mixture was warmed to 25°C, and was stirred for 14 hrs. The mixture was diluted with  
30 EtOAc, and was washed with water (3x) and brine, and was dried over MgSO<sub>4</sub>. Concentration gave a oil. To the solution of above oil in acetonitrile (2.5 mL) was added 48% HF/CH<sub>3</sub>CN (0.1 mL). The mixture was stirred for 30 minutes, and was diluted with EtOAc. The organic phase was washed with water (3x) and brine (1x), and was dried over

MgSO<sub>4</sub>. Purification by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/iPrOH = 100/3) gave compound 16 (50 mg): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.72 (2 H, d, J = 8.9 Hz), 7.15-7.05 (7 H, m), 7.30 (2 H, d, J = 8.9 Hz), 6.64 (2 H, m), 5.73 (1 H, m), 5.45 (1 H, m), 5.13 (1 H, m), 4.93 (1 H, m), 4.22-3.75 (11 H, m), 3.4 (4 H, m), 3.35-2.80 (5 H, m), 2.1-1.8 (3 H, m), 1.40-1.25 (6 H, m), 0.94 (6 H, m).

#### Example 17

Compound 17: To a solution of compound 16 (30 mg, 0.04 mmol) in EtOAc (0.8 mL) was added 37% formaldehyde (26 μL, 0.4 mmol). The mixture was cooled to 0°C, acetic acid (20 μL, 0.4 mmol) was added, followed by sodium cyanoborohydride (22 mg, 0.4 mmol). The mixture was warmed to 25°C, and was stirred for 14 hrs. The mixture was diluted with EtOAc, and was washed with water (3x) and brine, and was dried over MgSO<sub>4</sub>. Purification by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/iPrOH = 100/3) gave compound 17 (22 mg): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.63 (2 H, m), 7.3-6.9 (9 H, m), 6.79 (2 H, m), 5.68 (1 H, m), 5.2 (1 H, m), 5.10 (1 H, m), 4.95 (1 H, m), 4.22 (2 H, m), 4.2-3.7 (21 H, m), 2.0-1.7 (3 H, m), 1.4-1.2 (6 H, m), 0.93 (6 H, m).

Scheme 5



I. a. HCHO/100 °C; b. HCl/100 °C; c. HBr/120 °C; d. Boc<sub>2</sub>O/Na<sub>2</sub>CO<sub>3</sub> II. a. Tf<sub>2</sub>NPh/Cs<sub>2</sub>CO<sub>3</sub>; b. Bu<sub>3</sub>SnCH=CH<sub>2</sub>/LiCl/PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>/90 °C; III. a. NaIO<sub>4</sub>/OsO<sub>4</sub>; b. NaBH<sub>4</sub>; IV. a. CBr<sub>4</sub>/PPh<sub>3</sub>; b. (BnO)<sub>2</sub>POH/Cs<sub>2</sub>CO<sub>3</sub>; V. H<sub>2</sub>/10% Pd-C; VI. a. PhOH/DCC; b. NaOH; c. HCl; VII. Ethyl lactate/BOP; VIII. TFA/CH<sub>2</sub>Cl<sub>2</sub>; VIII. compound 15/NaBH<sub>3</sub>CN/HOAc.

Example 18

Compound 18: Compound 18 was purchased from Aldrich.

5

Example 19

Compound 19: To compound 18 (12.25 g, 81.1 mmol) was added 37% formaldehyde (6.15 mL, 82.7 mmol) slowly. The mixture was heated at 100°C for 1 hour. The mixture was cooled to 25°C, and was diluted with benzene, and was washed with water (2x).

Concentration under reduced pressure gave a yellow oil. To above oil was added 20% HCl (16 mL), and the mixture was heated at 100°C for 12 hours. The mixture was basified with 40% KOH solution at 0°C, and was extracted with EtOAc (3x). The combined organic layer was washed with water and brine, and was dried over MgSO<sub>4</sub>. Concentration gave a oil. To the oil was added 48% HBr (320 mL), and the mixture was heated at 120°C for 3 hours.

Water was removed at 100°C under reduced pressure to give a brown solid. To the solution of above solid in water/dioxane (200 mL/200mL) at 0°C was added sodium carbonate (25.7 g, 243 mmol) slowly, followed by di-tert-butyl dicarbonate (19.4 g, 89 mmol). The mixture was warmed to 25°C and stirred for 12 hours. Dioxane was removed under reduced pressure, and the remaining was extracted with EtOAc (3x). The combined organic phase was washed with water (3x) and brine, and was dried over MgSO<sub>4</sub>. Purification by flash column chromatography (hexanes/EtOAc = 4/1 to 3/1) gave compound 19 as white solid (13.6 g).

#### Example 20

Compound 20: To a solution of compound 19 (2.49 g, 10 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was added N-phenyltrifluoromethanesulfonimide (3.93 g, 11 mmol), followed by cesium carbonate (3.58 g, 11 mmol). The mixture was stirred for 48 hours. The solvent was removed under reduced pressure, and ethyl acetate was added. The reaction mixture was washed with water (3x) and brine (1x), and was dried over MgSO<sub>4</sub>. Purification by flash column chromatography (hexanes/EtOAc = 6/1) gave a white solid (3.3 g). To the solution of above solid (2.7 g, 7.1 mmol) in DMF (40 mL) was added lithium chloride (2.11 g, 49.7 mmol), followed by dichlorobis(triphenylphosphine) palladium(II) (100 mg, 0.14 mmol). The mixture was stirred for 3 minutes under high vacuum and recharged with nitrogen. To the above solution was added tributylvinyltin (2.07 mL, 7.1 mmol). The reaction mixture was heated at 90°C for 3 hours and cooled to 25°C. Water was added to the reaction, and the mixture was extracted with ethyl acetate (3X). The combined organic layer was washed with water (6x) and brine, and dried over MgSO<sub>4</sub>. Concentration gave an oil. The oil was diluted with CH<sub>2</sub>Cl<sub>2</sub> (5 mL), water (128 µL, 7.1mmol) and DBU (1 mL, 7.1 mmol) were added. The mixture was stirred for 5 minutes, and was subjected to flash column chromatography (hexanes/EtOAc = 9/1). Compound 20 was obtained as white solid (1.43 g).



Example 21

- Compound 21: To a solution of compound 20 (1.36 g, 5.25 mmol) in ethyl acetate (16 mL) was added water (16 mL), followed by 2.5% osmium tetroxide/tert-butanol (2.63 mL).
- 5 Sodium periodate (2.44 g) was added in portions over 2 minutes period. The mixture was stirred for 45 minutes, and was diluted with ethyl acetate. The organic layer was separated and washed with water (3x) and brine (1x), and dried over  $\text{MgSO}_4$ . Concentration gave a brown solid. To the solution of above solid in methanol (100 mL) at  $0^\circ\text{C}$  was added sodium borohydride. The mixture was stirred for 1 hour at  $0^\circ\text{C}$ , and was quenched with saturated
- 10  $\text{NH}_4\text{Cl}$  (40 mL). Methanol was removed under reduced pressure, and the remaining was extracted with EtOAc (3x). The combined organic layer was washed with water and brine, and was dried over  $\text{MgSO}_4$ . Purification by flash column chromatography (hexanes/EtOAc = 2/1) gave compound 21 (1.0 g).

15 Example 22

- Compound 22: To a solution of compound 21 (657 mg, 2.57 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) was added a solution of tetrabromocarbon (1.276 g, 3.86 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL). To the above mixture was added a solution of triphenylphosphine (673 mg, 2.57 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) over 30 minutes period. The mixture was stirred for 2 hours, and was concentrated under
- 20 reduced pressure. Purification by flash column chromatography (hexanes/EtOAc = 9/1) gave the bromide intermediate (549 mg). To the solution of above bromide (548 mg, 1.69 mmol) in acetonitrile (4.8 mL) was added dibenzyl phosphite (0.48 mL, 2.19 mmol), followed by cesium carbonate (828 mg, 2.54 mmol). The mixture was stirred for 48 hours, and was diluted with EtOAc.
- 25 The mixture was washed with water (3x) and brine, and was dried over  $\text{MgSO}_4$ . Purification by flash column chromatography (hexanes/EtOAc = 3/1 to 100% EtOAc) gave compound 22 (863 mg).

Example 23

- 30 Compound 23: To a solution of compound 22 (840 mg) in ethanol (80 mL) was added 10% palladium on carbon (200 mg). The mixture was hydrogenated for 2 hours. The mixture was stirred with celite for 5 mins, and was filtered through a pad of celite. Concentration under reduced pressure gave compound 23 (504 mg).

Example 24

Compound 24: To a solution of compound 23 (504 mg, 1.54 mmol) in pyridine (10.5 mL) was added phenol (1.45 g, 15.4 mmol), followed by DCC (1.28 g, 6.2 mmol). The mixture  
5 was heated at 65°C for 3 hours, and pyridine was removed under reduced pressure. The mixture was diluted with EtOAc (5 ml), and was filtered and washed with EtOAc (2x5 mL). Concentration gave a oil, which was purified by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/isopropanol = 100/3) to give diphenylphosphonate intermediate (340 mg). To a  
10 solution of above compound (341 mg, 0.71 mmol) in THF (1 mL) was added 0.85 mL of 1.0 N NaOH solution. The mixture was stirred at 25°C for 3 hours, and THF was removed under reduced pressure. The mixture was diluted with water, and was washed with EtOAc (3x), and then acidified with concentrated HCl until pH = 1. The aqueous was extracted with EtOAc (3x). The combined organic layer was washed with water (1x) and brine (1x), and dried over MgSO<sub>4</sub>. Concentration under reduced pressure gave compound 24 as a solid (270  
15 mg).

Example 25:

Compound 25: To a solution of compound 24 (230 mg, 0.57 mmol) in DMF (2 mL) was added ethyl (s)-lactate (130 µL, 1.14 mmol), followed by diisopropylethylamine (400 µL,  
20 2.28 mmol) and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (504 mg, 1.14 mmol). The mixture was stirred for 14 hours, was diluted with EtOAc. The organic phase was washed with water (5x) and brine (1x), and was dried over MgSO<sub>4</sub>. Purification by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/isopropanol = 100/3) gave compound 25 (220 mg).

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Example 26

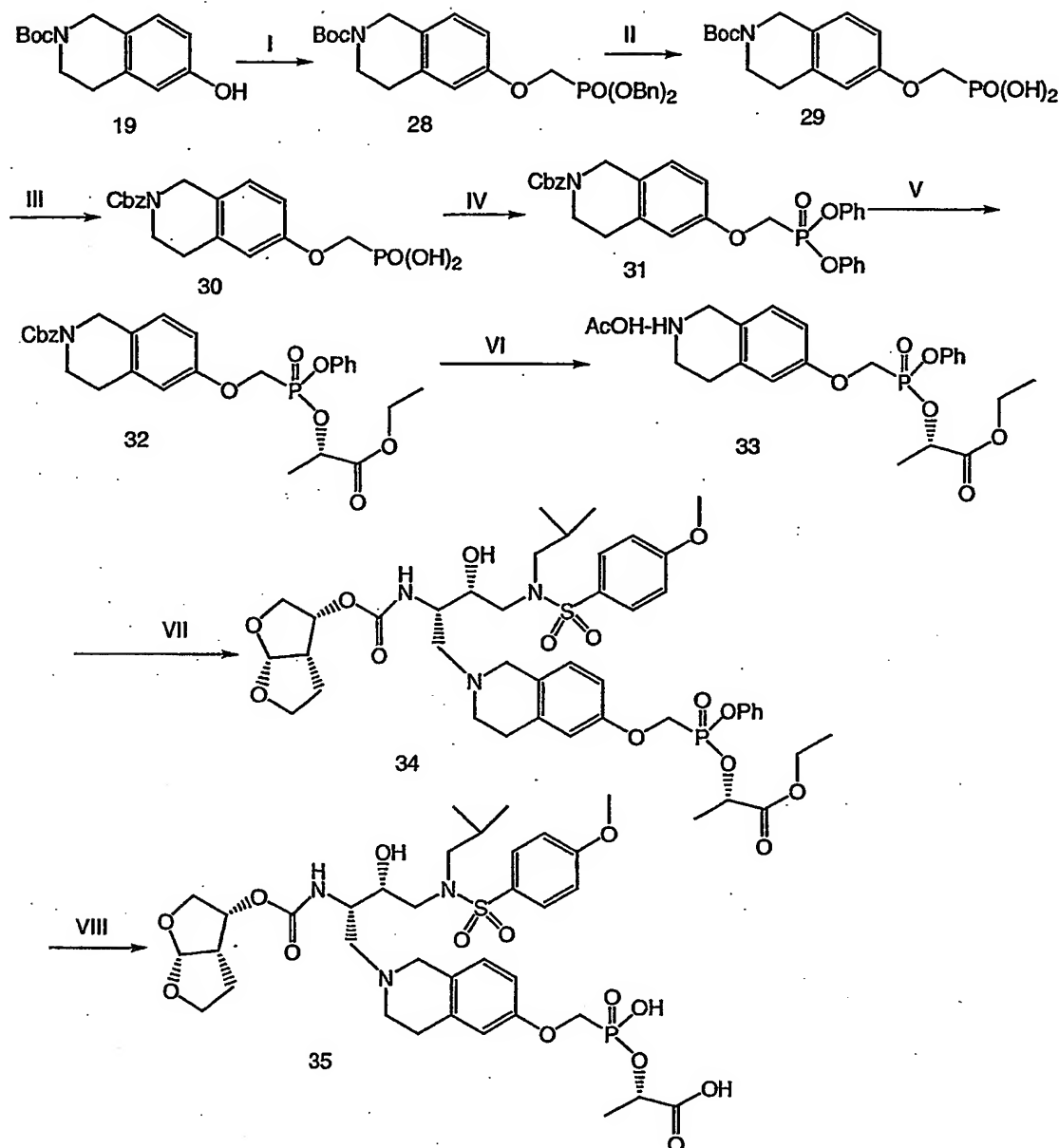
Compound 26: To a solution of compound 25 (220 mg) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added trifluoroacetic acid (1 mL). The mixture was stirred for 2 hrs, and was concentrated under reduced pressure. The mixture was diluted with EtOAc, and was washed with saturated  
30 sodium carbonate solution, water, and brine, and was dried over MgSO<sub>4</sub>. Concentration gave compound 26 (170 mg).

Example 27

Compound 27: To a solution of compound 15 (258 mg, 0.42 mmol) in EtOAc (2.6 mL) was added compound 26 (170 mg, 0.42 mmol), followed by acetic acid (75  $\mu$ L, 1.26 mmol). The mixture was stirred for 5 minutes, and sodium cyanoborohydride (53 mg, 0.84 mmol) was added. The mixture was stirred for 14 hrs. The mixture was diluted with EtOAc, and was washed with saturated sodium bicarbonate solution, water (3x) and brine, and was dried over MgSO<sub>4</sub>. Purification by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/iPrOH = 100/4 to 100/6) gave the intermediate (440 mg). To the solution of above compound (440 mg) in acetonitrile (10 mL) was added 48% HF/ CH<sub>3</sub>CN (0.4 mL). The mixture was stirred for 2 hours, and acetonitrile was removed under reduced pressure. The remaining was diluted with EtOAc, and was washed with water (3x) and brine (1x), and was dried over MgSO<sub>4</sub>. Purification by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/iPrOH = 100/5) gave compound 27 (120 mg): <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.70 (2 H, m), 7.27 (2 H, m), 7.15 (5 H, m), 6.95 (3 H, m), 5.73 (1 H, m), 5.6-5.4 (1 H, m), 5.16 (1 H, m), 4.96 (1 H, m), 4.22-3.60 (13 H, m), 3.42 (2 H, m), 3.4-2.6 (11 H, m), 2.1-3.8 (3 H, m), 1.39 (3 H, m), 1.24 (3 H, m), 0.84 (6 H, m).

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Scheme 6

**Example 28**

Compound 28: To a solution of compound 19 (7.5 g, 30 mmol) in acetonitrile (420 mL) was  
 5 added dibenzyl triflate (17.8 g, 42 mmol), followed by cesium carbonate (29.4 g, 90 mmol).

The mixture was stirred for 2.5 hours, and was filtered. Acetonitrile was removed under reduced pressure, and the remaining was diluted with EtOAc. The mixture was washed with water (3x) and brine, and was dried over MgSO<sub>4</sub>. Purification by flash column chromatography (hexanes/EtOAc = 2/1 to 1/1) gave compound 28 (14.3 g).

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#### Example 29

Compound 29: To a solution of compound 28 (14.3 g) in ethanol (500 mL) was added 10% palladium on carbon (1.45 g). The mixture was hydrogenated for 2 hours. The mixture was stirred with celite for 5 mins, and was filtered through a pad of celite. Concentration under reduced pressure gave compound 29 (9.1 g).

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#### Example 30

Compound 30: To a solution of compound 29 (9.1 g) in CH<sub>2</sub>Cl<sub>2</sub> (60 mL) was added trifluoroacetic acid (30 mL). The mixture was stirred for 4 hrs, and was concentrated under reduced pressure. The mixture was coevaporated with CH<sub>2</sub>Cl<sub>2</sub> (3x) and toluene, and was dried under high vacuum to give a white solid. The white solid was dissolved in 2.0 N NaOH solution (45 mL, 90 mmol), and was cooled to 0°C. To the above solution was added slowly a solution of benzyl chloroformate (6.4 mL, 45 mmol) in toluene (7 mL). The mixture was warmed to 25°C, and was stirred for 6 hours. 2.0 N sodium hydroxide was added to above solution until pH = 11. The aqueous was extracted with ethyl ether (3x), and was cooled to 0°C. To the above aqueous phase at 0°C was added concentrated HCl until pH = 1. The aqueous was extracted with EtOAc (3x). The combine organic layers were washed with brine, and were dried over MgSO<sub>4</sub>. Concentration gave compound 30 (11.3 g) as a white solid.

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#### Example 31

Compound 31: To the suspension of compound 30 (11.3 g, 30 mmol) in toluene (150 mL) was added thionyl chloride (13 mL, 180 mmol), followed by DMF (a few drops). The reaction mixture was heated at 65°C for 4.5 hrs, and evaporated under reduced pressure. The mixture was coevaporated with toluene (2x) to afford a brown solid. To the solution of the brown solid in CH<sub>2</sub>Cl<sub>2</sub> (120 mL) at 0°C was added phenol (11.28 g, 120 mmol), followed by slow addition of pyridine (14.6 mL, 180 mmol). The reaction mixture was allowed to warm to 25°C and stirred for 14 hrs. Solvents were removed under reduced pressure. The mixture

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was diluted with EtOAc, and washed with water (3x) and brine (1x), and dried over MgSO<sub>4</sub>. Concentration gave a dark oil, which was purified by flash column chromatography (hexanes/EtOAc = 3/1 to 1/1) to afford compound 31 (9.8 g).

5    Example 32

Compound 32: To a solution of compound 31 (9.8 g, 18.5 mmol) in THF (26 mL) was added 20.3 mL of 1.0 N NaOH solution. The mixture was stirred at 25°C for 2.5 hours, and THF was removed under reduced pressure. The mixture was diluted with water, and was washed with EtOAc (3x). The aqueous phase was cooled to 0°C, and was acidified with concentrated HCl until pH = 1. The aqueous was extracted with EtOAc (3x). The combined organic layer was washed with water (1x) and brine (1x), and dried over MgSO<sub>4</sub>. Concentration under reduced pressure gave a solid (8.2 g). To a suspension of above solid (4.5 g, 10 mmol) in toluene (50 mL) was added thionyl chloride (4.4 mL, 60 mmol), followed by DMF (0.2 mL). The mixture was heated at 70°C for 3.5 hours. The solvent and reagent were removed under reduced pressure. The mixture was coevaporated with toluene (2x) to give a white solid. To the solution of the above solid in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) at 0°C was added ethyl (s)-lactate (2.3 mL, 20 mmol), followed by pyridine (3.2 mL, 40 mmol). The mixture was warmed to 25°C and stirred for 12 hours. The reaction mixture was concentrated under reduced pressure, and was diluted with EtOAc. The organic phase was washed with 1 N HCl, water, and brine, and was dried over MgSO<sub>4</sub>. Purification by flash column chromatography (hexanes/EtOAc = 2/1 to 1/1) gave compound 32 (4.1 g).

Example 33

Compound 33: To a solution of compound 32 (3.8 g, 6.9 mmol) in EtOAc/EtOH (30 mL/30 mL) was added 10% palladium on carbon (380 mg), followed by acetic acid (400 µL, 6.9 mmol). The mixture was hydrogenated for 3 hours. The mixture was stirred with celite for 5 mins, and was filtered through a pad of celite. Concentration under reduced pressure gave compound 33 (3.5 g).

30    Example 34

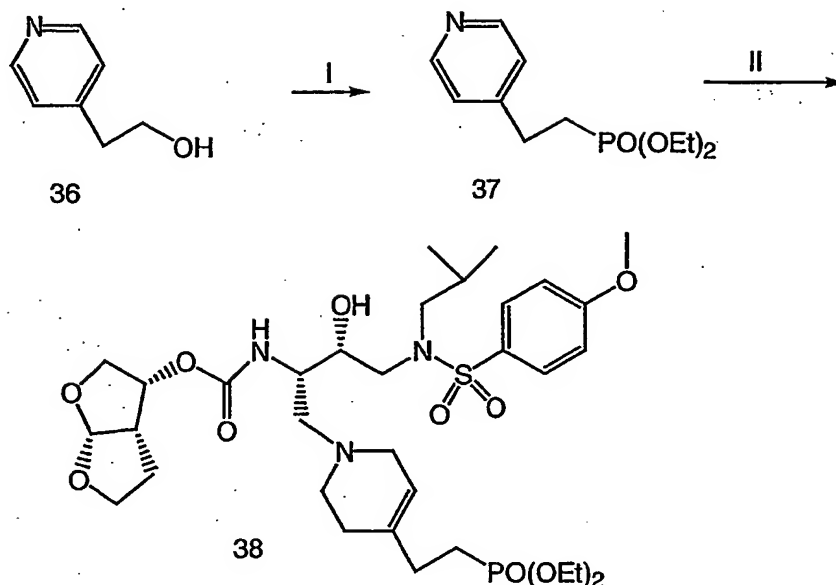
Compound 34: To a solution of compound 15 (1.70 g, 2.76 mmol) in EtOAc (17 mL) was added compound 33 (3.50 g, 6.9 mmol). The mixture was stirred for 5 minutes, and was cooled to 0°C, and sodium cyanoborohydride (347 mg, 5.52 mmol) was added. The mixture

was stirred for 6 hrs. The mixture was diluted with EtOAc, and was washed with saturated sodium bicarbonate solution, water (3x) and brine, and was dried over MgSO<sub>4</sub>. Purification by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/iPrOH = 100/6) gave the intermediate (3.4 g). To the solution of above compound (3.4 g) in acetonitrile (100 mL) was added 48% HF/ CH<sub>3</sub>CN (4 mL). The mixture was stirred for 2 hours, and acetonitrile was removed under reduced pressure. The remaining was diluted with EtOAc, and was washed with saturated sodium carbonate, water (3x), and brine (1x), and was dried over MgSO<sub>4</sub>. Purification by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/iPrOH = 100/5) gave compound 34 (920 mg): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.71 (2 H, m), 7.38-7.19 (5 H, m), 6.92 (3 H, m), 6.75 (2 H, m), 5.73 (1 H, m), 5.57-5.35 (1 H, m), 5.16 (2 H, m), 4.5 (2 H, m), 4.2-3.6 (13 H, m), 3.25-2.50 (11 H, m), 2.0-1.8 (3 H, m), 1.5 (3 H, m), 1.23 (3 H, m), 0.89 (6 H, m).

#### Example 35

Compound 35: To a solution of compound 34 (40 mg) in CH<sub>3</sub>CN /DMSO (1 mL/0.5 mL) was added 1.0 M PBS buffer (5 mL), followed by esterase (200 μL). The mixture was heated at 40°C for 48 hours. The mixture was purified by reverse phase HPLC to give compound 35 (11 mg).

## Scheme 7



I. a.  $\text{SOCl}_2$ /toluene/60 C; b.  $\text{P}(\text{OEt})_3$ /toluene/120 C;  
 II. a. compound 14/ $\text{Ti}_2\text{O}_3$ ; b.  $\text{NaBH}_4$ /EtOH/HOAc; c. 2% HF/ $\text{CH}_3\text{CN}$

Example 36

Compound 36: Compound 36 was purchased from Aldrich.

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Example 37

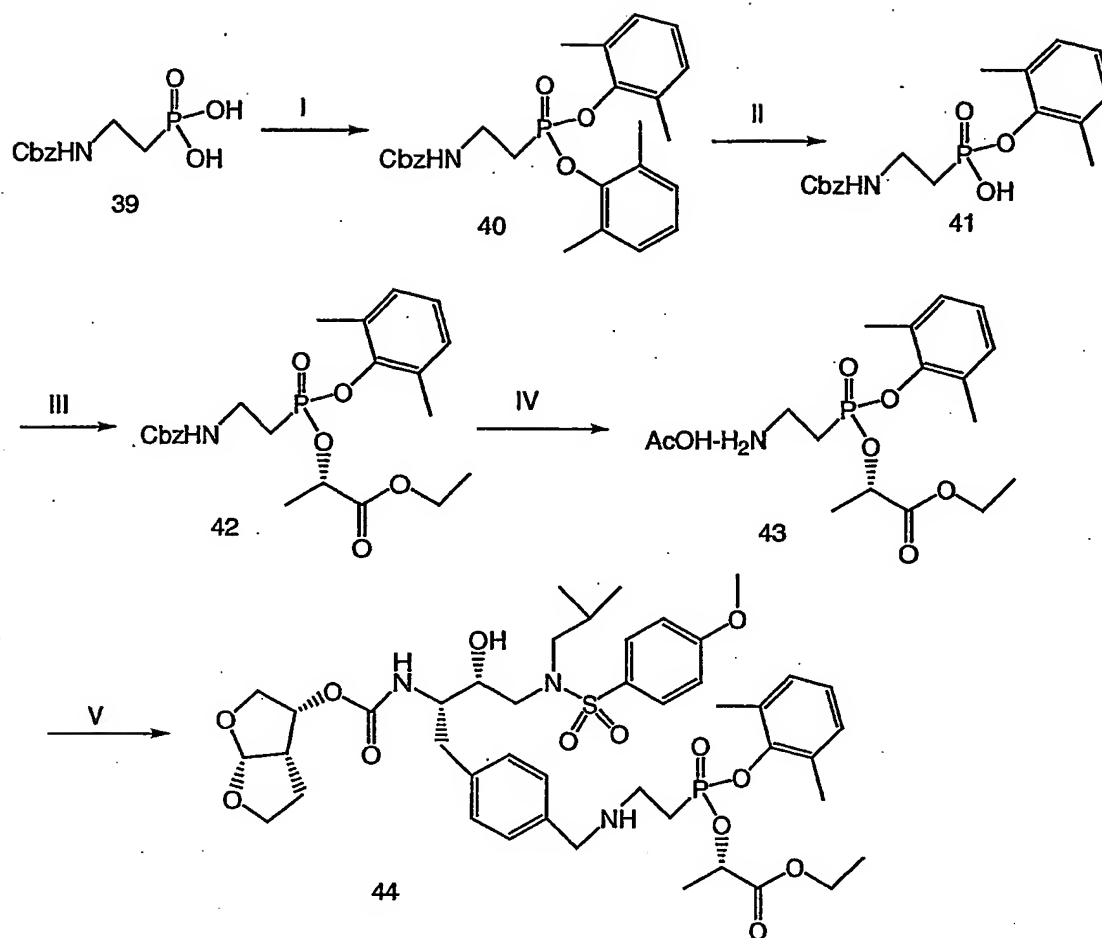
Compound 37: To a solution of compound 36 (5.0 g, 40 mmol) in chloroform (50 mL) was added thionyl chloride (12 mL) slowly. The mixture was heated at 60°C for 2.5 hours. The mixture was concentrated under reduced pressure to give a yellow solid. To the suspension of above solid (5.2 g, 37 mmol) in toluene (250 mL) was added triethyl phosphite (19 mL, 370 mmol). The mixture was heated at 120°C for 4 hours, and was concentrated under reduced pressure to give a brown solid. The solid was dissolved in EtOAc, and was basified with 1.0 N NaOH. The organic phase was separated and was washed with water (2x) and brine, and was dried over  $\text{MgSO}_4$ . Purification by flash column chromatography (10  
 15  $\text{CH}_2\text{Cl}_2/\text{iPrOH} = 9/1$ ) gave compound 37 (4.8 g).



Example 38

Compound 38: To a solution of compound 14 (100 mg, 0.16 mmol) and compound 37 (232 mg, 0.74 mmol) in  $\text{CH}_2\text{Cl}_2$  (1 mL) at  $-40^\circ\text{C}$  was added triflic anhydride (40  $\mu\text{L}$ , 0.24 mmol) slowly. The mixture was warmed to  $25^\circ\text{C}$  slowly, and was stirred for 12 hours. The mixture  
5 was concentrated, and was diluted with EtOH/EtOAc (2 mL/0.4 mL). To the above solution at  $0^\circ\text{C}$  was added sodium borohydride (91 mg) in portions. The mixture was stirred at  $0^\circ\text{C}$  for 3 hours, and was diluted with EtOAc. The mixture was washed with saturated sodium bicarbonate, water, and brine, and was dried over  $\text{MgSO}_4$ . Purification by flash column chromatograph ( $\text{CH}_2\text{Cl}_2/\text{iPrOH} = 100/5$  to  $100/10$ ) gave the intermediate (33 mg). To the  
10 solution of above intermediate in acetonitrile (2.5 mL) was added 48% HF/  $\text{CH}_3\text{CN}$  (0.1 mL). The mixture was stirred for 30 minutes, and was diluted with EtOAc. The organic solution was washed with 0.5 N sodium hydroxide, water, and brine, was dried over  $\text{MgSO}_4$ .  
Purification by reverse HPLC gave compound 38 (12 mg):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.72 (2 H, d,  $J = 8.9$  Hz), 7.02 (2 H, d,  $J = 8.9$  Hz), 5.70 (1 H, m), 5.45 (1 H, m), 5.05 (1 H, m), 4.2-3.4 (19  
15 H, m), 3.4-2.8 (5 H, m), 2.45-2.20 (4 H, m), 2.15-1.81 ( 5 H, m), 1.33 (6 H, m), 0.89 (6 H, m).

Scheme 8



I. a.  $\text{SOCl}_2$ /toluene/60 °C; b. ArOH/pyridine; II. a. NaOH/THF/ $\text{H}_2\text{O}$ ; b. HCl;  
 III. b.  $\text{SOCl}_2$ /toluene/60 °C; c. ethyl lactate/pyridine; IV.  $\text{H}_2$ /10% Pd-C/EtOAc/HOAc;  
 V. a. compound 6/ $\text{MgSO}_4$ ; b. HOAc/ $\text{NaCNBH}_3$

#### Example 39

Compound 39 was prepared by the methods of the previous Examples.

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#### Example 40

Compound 40: To the suspension of compound 39 (4.25 g, 16.4 mmol) in toluene (60 mL) was added thionyl chloride (7.2 mL, 99 mmol), followed by DMF (a few drops). The reaction mixture was heated at 65°C for 5 hrs, and evaporated under reduced pressure. The mixture was coevaporated with toluene (2x) to afford a brown solid. To the solution of the brown solid in  $\text{CH}_2\text{Cl}_2$  (60 mL) at 0°C was added 2,6-dimethylphenol (8.1 g, 66 mmol),

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followed by slow addition of pyridine (8 mL, 99 mmol). The reaction mixture was allowed to warm to 25°C and stirred for 14 hrs. Solvents were removed under reduced pressure. The mixture was diluted with EtOAc, and washed with water (3x) and brine (1x), and dried over MgSO<sub>4</sub>. Purification by flash column chromatography (hexanes/EtOAc = 3/1 to 1/1) afforded compound 40 (1.38 g).

#### Example 41

Compound 41: To a solution of compound 40 (1.38 g, 1.96 mmol) in THF (6 mL) was added 3.55 mL of 1.0 N NaOH solution. The mixture was stirred at 25°C for 24 hours, and THF was removed under reduced pressure. The mixture was diluted with water, and was washed with EtOAc (3x). The aqueous phase was cooled to 0°C, and was acidified with concentrated HCl until pH = 1. The aqueous was extracted with EtOAc (3x). The combined organic layer was washed with water (1x) and brine (1x), and dried over MgSO<sub>4</sub>. Concentration under reduced pressure gave compound 41 as a white solid (860 mg).

#### Example 42

Compound 42: To a suspension of compound 41 (1.00 g, 2.75 mmol) in toluene (15 mL) was added thionyl chloride (1.20 mL, 16.5 mmol), followed by DMF (3 drops). The mixture was heated at 65°C for 5 hours. The solvent and reagent were removed under reduced pressure. The mixture was coevaporated with toluene (2x) to give a brown solid. To the solution of the above solid in CH<sub>2</sub>Cl<sub>2</sub> (11 mL) at 0°C was added ethyl (s)-lactate (1.25, 11 mmol), followed by pyridine (1.33 mL, 16.6 mmol). The mixture was warmed to 25°C and stirred for 12 hours. The reaction mixture was concentrated under reduced pressure, and was diluted with EtOAc. The organic phase was washed with 1 N HCl, water, and brine, and was dried over MgSO<sub>4</sub>. Purification by flash column chromatography (hexanes/EtOAc = 1.5/1 to 1/1) gave compound 42 (470 mg).

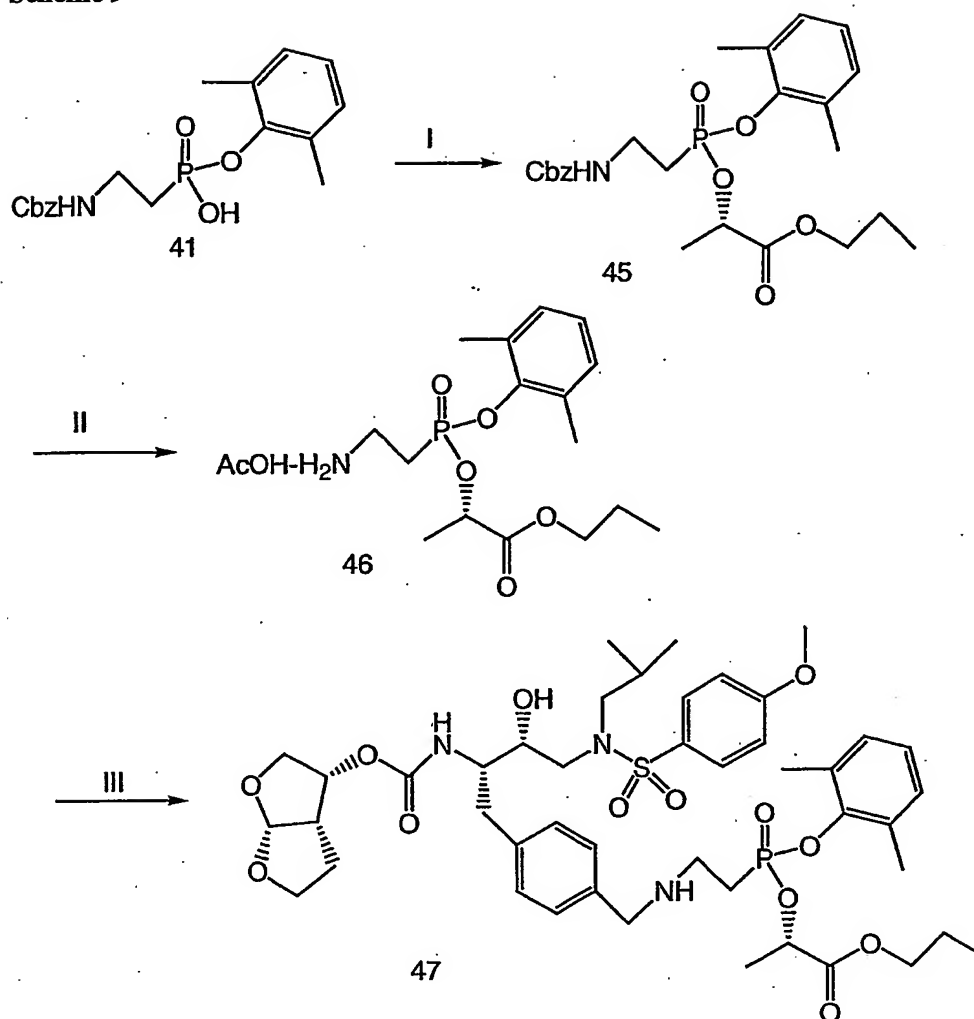
#### Example 43

Compound 43: To a solution of compound 42 (470 mg) in EtOH (10 mL) was added 10% palladium on carbon (90 mg), followed by acetic acid (150 µL). The mixture was hydrogenated for 6 hours. The mixture was stirred with celite for 5 mins, and was filtered through a pad of celite. Concentration under reduced pressure gave compound 43 (400 mg).

Example 44

Compound 44: To a solution of compound 6 (551 mg, 0.93 mmol) in 1,2-dichloroethane (4 mL) was added compound 43 (400 mg, 1.0 mmol), followed by  $\text{MgSO}_4$  (1 g). The mixture was stirred for 3 hours, and acetic acid (148  $\mu\text{L}$ ) and sodium cyanoborohydride (117 mg, 1.86 mmol) were added sequentially. The mixture was stirred for 1 hour. The mixture was diluted with EtOAc, and was washed with saturated sodium bicarbonate solution, water (3x) and brine, and was dried over  $\text{MgSO}_4$ . Purification by flash column chromatography (EtOAc to EtOAc/EtOH = 9/1) gave compound 44. Compound 44 was dissolved in  $\text{CH}_2\text{Cl}_2$  (25 mL), and trifluoroacetic acid (100  $\mu\text{L}$ ) was added. The mixture was concentrated to give compound 44 as a TFA salt (560 mg):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.74 (2 H, m), 7.39 (2 H, m), 7.20 (2 H, m), 7.03 (5 H, m), 5.68 (1 H, m), 5.43 (1 H, m), 5.01 (1 H, m), 4.79 (1 H, m), 4.35-4.20 (4 H, m), 4.18-3.4 (11 H, m), 3.2-2.6 (9 H, m), 2.30 (6 H, m), 1.82 (1 H, m), 1.70 (2 H, m), 1.40-1.18 (6 H, m), 0.91 (6 H, m).

## Scheme 9



I. b.  $\text{SOCl}_2$ /toluene/60 °C; c. propyl (S)-lactate/pyridine;  
 II.  $\text{H}_2$ /10%Pd-C/EtOAc/HOAc;  
 III. a. compound 6/ $\text{MgSO}_4$ ; b. HOAc/ $\text{NaCNBH}_3$

Example 45

Compound 45: To a suspension of compound 41 (863 mg, 2.4 mmol) in toluene (13 mL) was added thionyl chloride (1.0 mL, 14.3 mmol), followed by DMF (3 drops). The mixture was heated at 65°C for 5 hours. The solvent and reagent were removed under reduced pressure. The mixture was coevaporated with toluene (2x) to give a brown solid. To the solution of the above solid in  $\text{CH}_2\text{Cl}_2$  (10 mL) at 0°C was added propyl (S)-lactate (1.2 mL, 9.6 mmol), followed by triethylamine (2.0 mL, 14.4 mmol). The mixture was warmed to 25°C and stirred for 12 hours. The reaction mixture was concentrated under reduced pressure, and was

diluted with EtOAc. The organic phase was washed with water and brine, and was dried over  $\text{MgSO}_4$ . Purification by flash column chromatography (hexanes/EtOAc = 1.5/1 to 1/1) gave compound 45 (800 mg).

5    Example 46

Compound 46: To a solution of compound 45 (785 mg) in EtOH (17 mL) was added 10% palladium on carbon (150 mg), followed by acetic acid (250  $\mu\text{L}$ ). The mixture was hydrogenated for 16 hours. The mixture was stirred with celite for 5 mins, and was filtered through a pad of celite. Concentration under reduced pressure gave compound 46 (700 mg).

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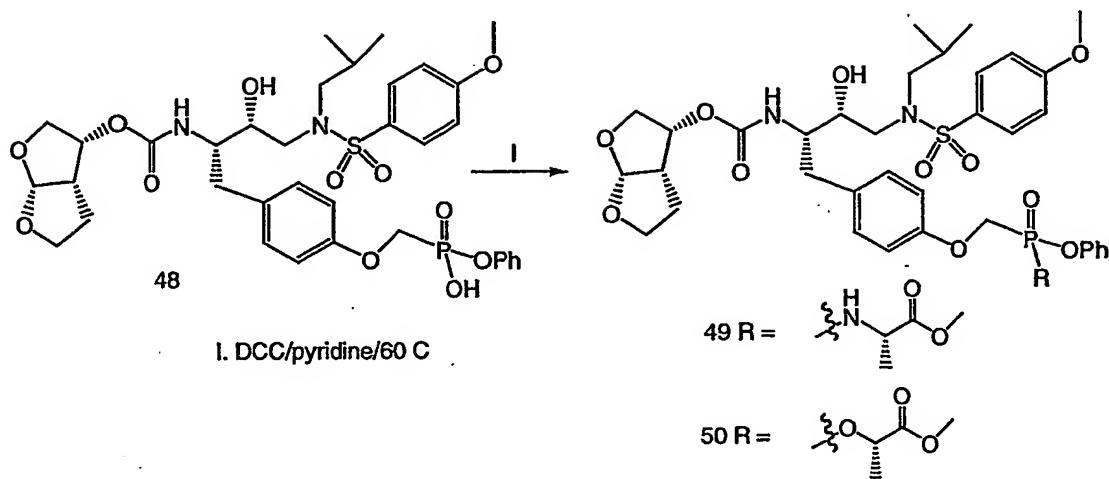
Example 47

Compound 47: To a solution of compound 6 (550 mg, 0.93 mmol) in 1,2-dichloroethane (4 mL) was added compound 43 (404 mg, 1.0 mmol), followed by  $\text{MgSO}_4$  (1 g). The mixture was stirred for 3 hours, and acetic acid (148  $\mu\text{L}$ ) and sodium cyanoborohydride (117 mg, 1.86 mmol) were added sequentially. The mixture was stirred for 1 hour. The mixture was diluted with EtOAc, and was washed with saturated sodium bicarbonate solution, water (3x) and brine, and was dried over  $\text{MgSO}_4$ . Purification by flash column chromatography (EtOAc to EtOAc/EtOH = 9/1) gave compound 47. Compound 47 was dissolved in  $\text{CH}_2\text{Cl}_2$  (25 mL), and trifluoroacetic acid (100  $\mu\text{L}$ ) was added. The mixture was concentrated to give compound 47 as a TFA salt (650 mg):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.74 (2 H, m), 7.41 (2 H, m), 7.25-7.1 (2 H, m), 7.02 (5 H, m), 5.65 (1 H, m), 5.50 (1 H, m), 5.0-4.75 (2 H, m), 4.25-4.05 (4 H, m), 4.0-3.4 (11 H, m), 3.2-2.6 (9 H, m), 2.31 (6 H, m), 1.82-1.51 (3 H, m), 1.45-1.2 (5 H, m), 0.93 (9 H, m).

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Scheme 10

Example 48

Compound 48 was made by the methods of the previous Examples.

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Example 49

Compound 49: To a solution of compound 48 (100 mg, 0.13 mmol) in pyridine (0.75 mL) was added L-alanine methyl ester hydrochloride (73 mg, 0.52 mmol), followed by DCC (161 mg, 0.78 mmol). The mixture was heated at 60°C for 1 hour. The mixture was diluted with EtOAc, and was washed with 0.2 N HCl, water, 5% sodium bicarbonate, and brine, and was dried over MgSO<sub>4</sub>. Purification by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/iPrOH = 100/5) gave compound 49 (46 mg): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.73 (2 H, m), 7.38-7.18 (7 H, m), 7.03 (2 H, m), 6.89 (2 H, m), 5.68 (1 H, m), 5.05 (1 H, m), 4.95 (1 H, m), 4.30 (3 H, m), 4.0-3.6 (12 H, m), 3.2-2.8 (7 H, m), 1.84-1.60 (3 H, m), 1.38 (3 H, m), 0.93 (6 H, m).

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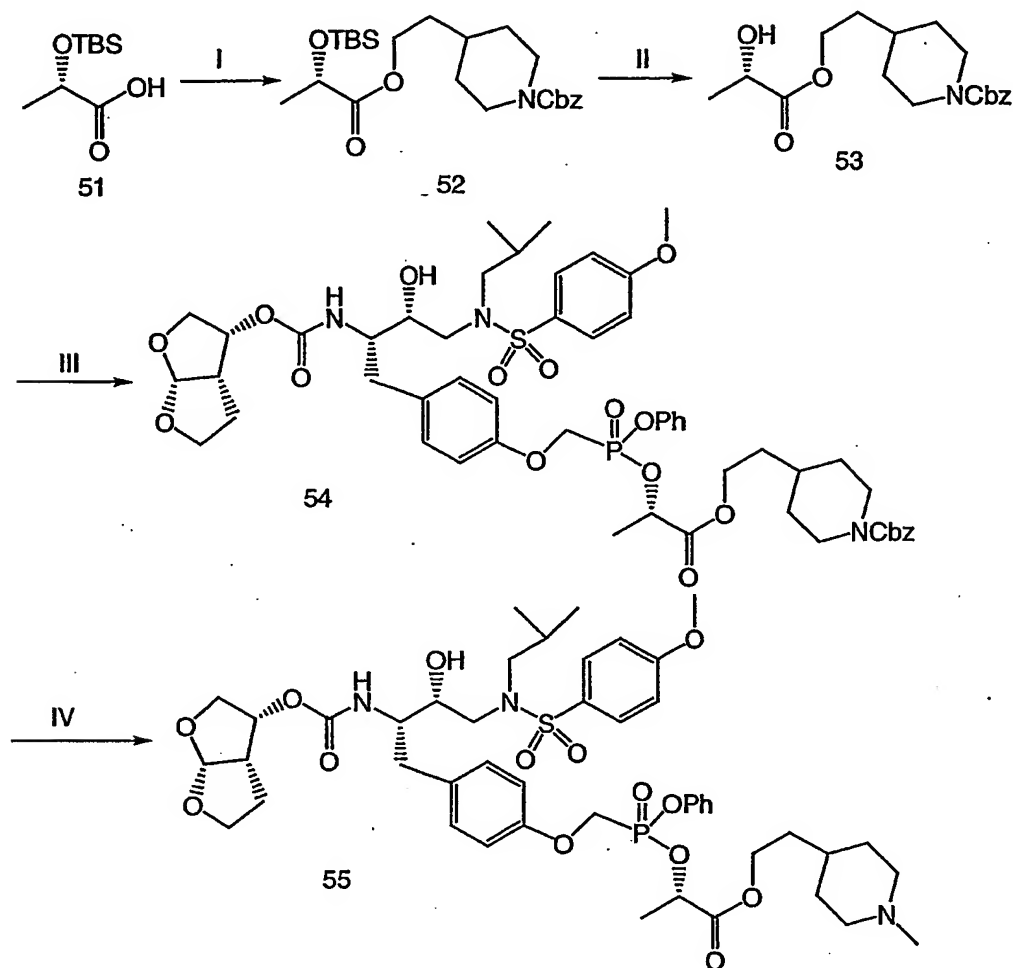
Example 50

Compound 50: To a solution of compound 48 (100 mg, 0.13 mmol) in pyridine (0.75 mL) was added methyl (s)-lactate (41 mg, 0.39 mmol), followed by DCC (81 mg, 0.39 mmol). The mixture was heated at 60°C for 2 hours, and pyridine was removed under reduced pressure. The mixture was diluted with EtOAc (5 mL), and was filtered. Purification by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/iPrOH = 100/5) gave compound 50 (83 mg): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.74 (2 H, m), 7.38-7.14 (7 H, m), 7.02 (2 H, m), 6.93 (2 H, m), 5.67 (1 H,

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m), 5.18 (1 H, m), 5.04 (1 H, m), 4.92 (1 H, m), 4.5 (2 H, m), 4.0-3.68 (12 H, m), 3.2-2.75 (7 H, m), 1.82 (1 H, m), 1.75-1.50 (5 H, m), 0.93 (6 H, m).

Scheme 11



I. Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate/ROH/ $i\text{Pr}_2\text{NEt}$ ;  
 II. 15% HF/ $\text{CH}_3\text{CN}$ ; III. Compound 48/DCC/pyridine/60 °C; IV. a.  $\text{H}_2$ /10% Pd-C;  
 b.  $\text{NaBH}_3\text{CN}$ /HCHO/HOAc

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### Example 51

Compound 51: To a solution of benzyl (S)-lactate (4.0 g, 20 mmol) in DMF (40 mL) was added imidazole (2.7 g, 20 mmol), followed by tert-butyldimethylsilyl chloride (3.3 g, 22 mmol). The mixture was stirred for 14 hours, and diluted with EtOAc. The organic phase  
 10 was washed with 1.0 N HCl solution (2x), water (2x), and brine (1x), and dried over  $\text{MgSO}_4$ .



Concentration gave the lactate intermediate (6.0 g). To the solution of the above intermediate in EtOAc (200 mL) was added 10% Palladium on carbon (700 mg). The mixture was hydrogenated for 2 hours. The mixture was stirred with celite for 5 minutes, and was filtered through a pad of celite. Concentration gave compound 51 (3.8 g).

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#### Example 52

Compound 52: To a solution of compound 51 (1.55 g, 7.6 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 mL) was added 4-benzyloxycarbonylpiperidineethanol (2.00 g, 7.6 mmol), followed by benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (4.74 g, 9.1 mmol) and diisopropylethylamine (1.58 mL, 9.1 mmol). The mixture was stirred for 14 hours, and dichloromethane was removed. The mixture was diluted with EtOAc, and was washed with brine, and dried with  $\text{MgSO}_4$ . Purification by flash column chromatography (hexanes/EtOAc = 10/1) gave compound 52 (1.50 g).

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#### Example 53

Compound 53: To a solution of compound 52 (1.50 g) in  $\text{CH}_3\text{CN}$  was added 58%  $\text{HF}/\text{CH}_3\text{CN}$  (5 mL). The mixture was stirred for 30 minutes, and acetonitrile was removed under reduced pressure. The mixture was diluted with EtOAc, and was washed with water and brine, and was dried over  $\text{MgSO}_4$ . Purification by flash column chromatography (hexanes/EtOAc = 1/1) gave compound 53 (1.00 g).

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#### Example 54

Compound 54: To a solution of compound 48 (769 mg, 1.0 mmol) in pyridine (6.0 mL) was added compound 53 (1.0 g, 3.0 mmol), followed by DCC (618 mg, 3.0 mmol). The mixture was heated at  $60^\circ\text{C}$  for 2 hours, and pyridine was removed under reduced pressure. The mixture was diluted with EtOAc (5 mL), and was filtered. Purification by flash column chromatography ( $\text{CH}_2\text{Cl}_2/\text{iPrOH}$  = 100/4) gave compound 54 (630 mg).

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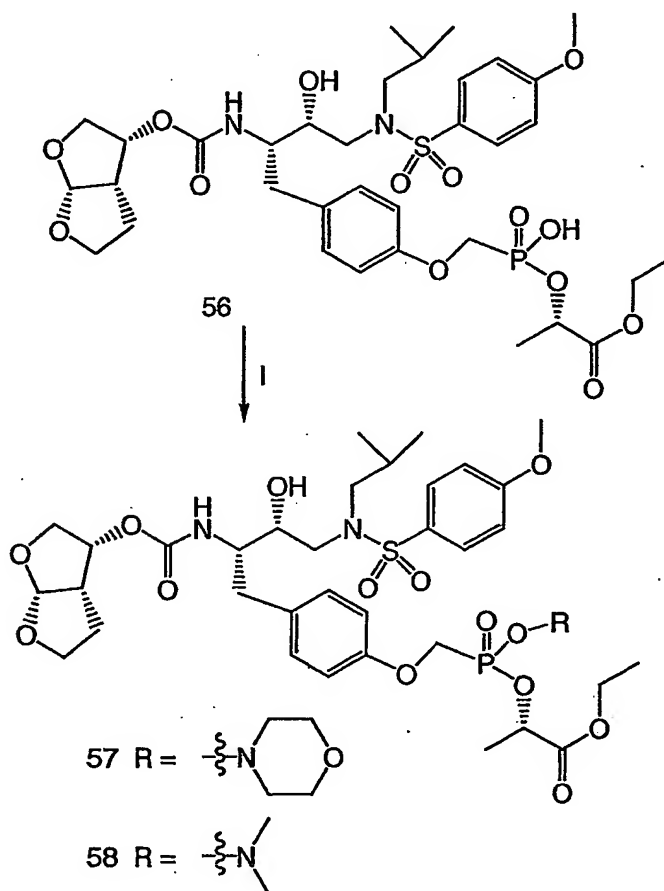
#### Example 55

Compound 55: To a solution of compound 54 (630 mg, 0.58 mmol) in EtOAc (30 mL) was added 10% Palladium on carbon (63 mg), followed by acetic acid (80  $\mu\text{L}$ ). The mixture was hydrogenated for 2 hours. The mixture was stirred with celite for 5 minutes, and was filtered through a pad of celite. Concentration gave the intermediate. To the solution of the above

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intermediate in EtOAc (10 mL) was added 37% formaldehyde (88  $\mu$ L, 1.18 mmol), followed by acetic acid (101  $\mu$ L, 1.77 mmol). The mixture was cooled to 0°C, and sodium cyanoborohydride (74 mg, 1.18 mmol) was added. The mixture was stirred at 25°C for 80 minutes, and was diluted with EtOAc. The mixture was washed with water and brine, and was dried over MgSO<sub>4</sub>. Concentration gave compound 55 as a white solid (530 mg): <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.74 (2 H, m), 7.40-7.15 (7 H, m), 7.03 (2 H, m), 6.92 (2 H, m), 5.66 (1 H, m), 5.20-5.00 (3 H, m), 4.58-4.41 (2 H, m), 4.16 (2 H, m), 4.0-3.7 (9 H, m), 3.4-2.6 (14 H, m), 1.90-1.50 (13 H, m), 0.92 (6 H, m).

Scheme 12



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I. R<sub>2</sub>NOH/DCC/pyridineExample 56

Compound 56 was made by the methods of the previous Examples.

Example 57

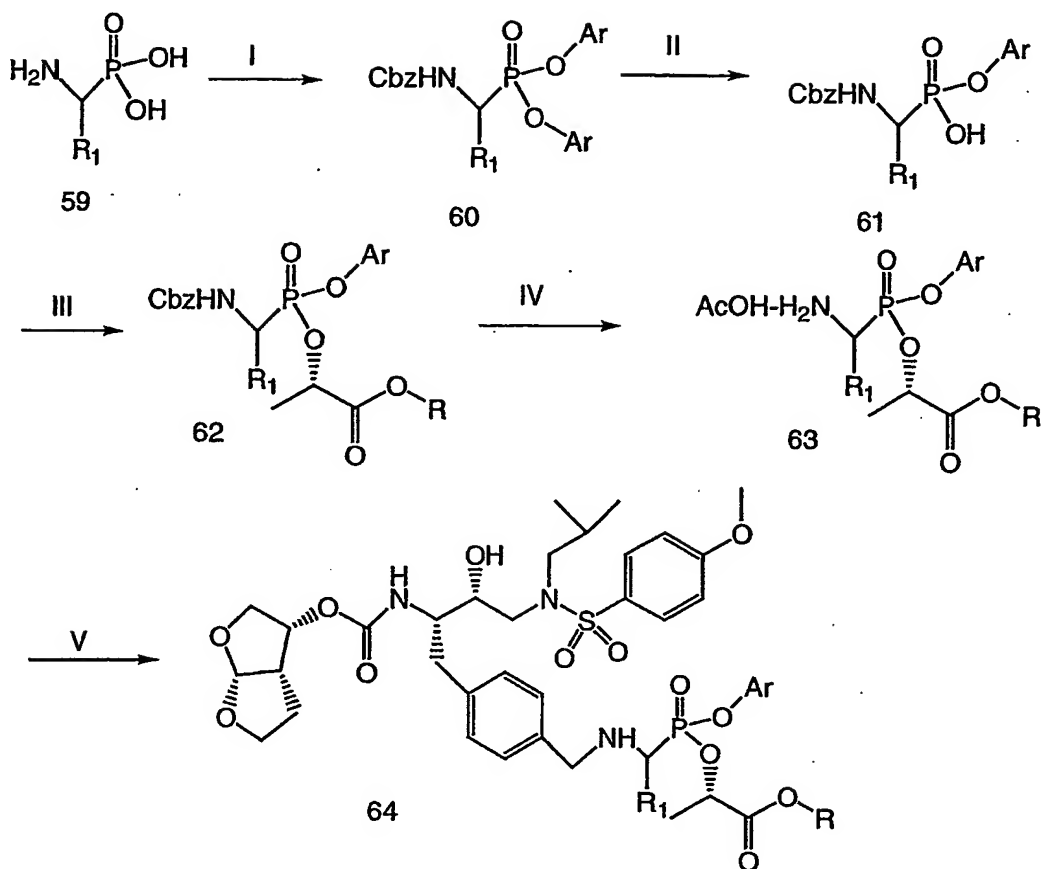
Compound 57: To a solution of compound 56 (100 mg, 0.12 mmol) in pyridine (0.6 mL) was added N-hydroxymorpholine (50 mg, 0.48 mmol), followed by DCC (99 mg, 0.48 mmol).

- 5 The mixture was stirred for 14 hours, and pyridine was removed under reduced pressure. The mixture was diluted with EtOAc, and was filtered. Purification by flash column chromatography ( $\text{CH}_2\text{Cl}_2/\text{iPrOH} = 100/5$ ) gave compound 57 (53 mg):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71 (2 H, d,  $J = 8.6$  Hz), 7.15 (2 H, d,  $J = 7.6$  Hz), 6.99 (2 H, d,  $J = 8.8$  Hz), 6.90 (2 H, m), 5.67 (1 H, m), 5.18 (1 H, m), 5.05 (1 H, m), 4.95 (1 H, m), 4.58-4.38 (2 H, m), 4.21 (2 H, m),  
10 4.02-3.80 (13 H, m), 3.55-3.38 (2 H, m), 3.2-2.78 (9 H, m), 1.9-1.8 (1 H, m), 1.8-0.95 (5 H, m), 1.29 (3 H, m), 0.93 (6 H, m).

Example 58

Compound 58: To a solution of compound 56 (100 mg, 0.12 mmol) in pyridine (0.6 mL) was  
15 added N,N-dimethylhydroxylamine hydrochloride (47 mg, 0.48 mmol), followed by DCC (99 mg, 0.48 mmol). The mixture was stirred for 6 hours, and pyridine was removed under reduced pressure. The mixture was diluted with EtOAc, and was filtered. Purification by flash column chromatography ( $\text{CH}_2\text{Cl}_2/\text{iPrOH} = 100/5$ ) gave compound 58 (35 mg).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71 (2 H, d,  $J = 8.9$  Hz), 7.15 (2 H, d,  $J = 8.2$  Hz), 6.99 (2 H, d,  $J = 8.4$  Hz), 6.89  
20 (2 H, m), 5.65 (1 H, d,  $J = 5.2$  Hz), 5.15 (1 H, m), 4.98 (2 H, m), 4.42 (2 H, m), 4.18 (2 H, m), 4.0-3.6 (9 H, m), 3.2-2.7 (13 H, m), 1.92-1.45 (6 H, m), 1.25 (3 H, m), 0.90 (6 H, m).

Scheme 13



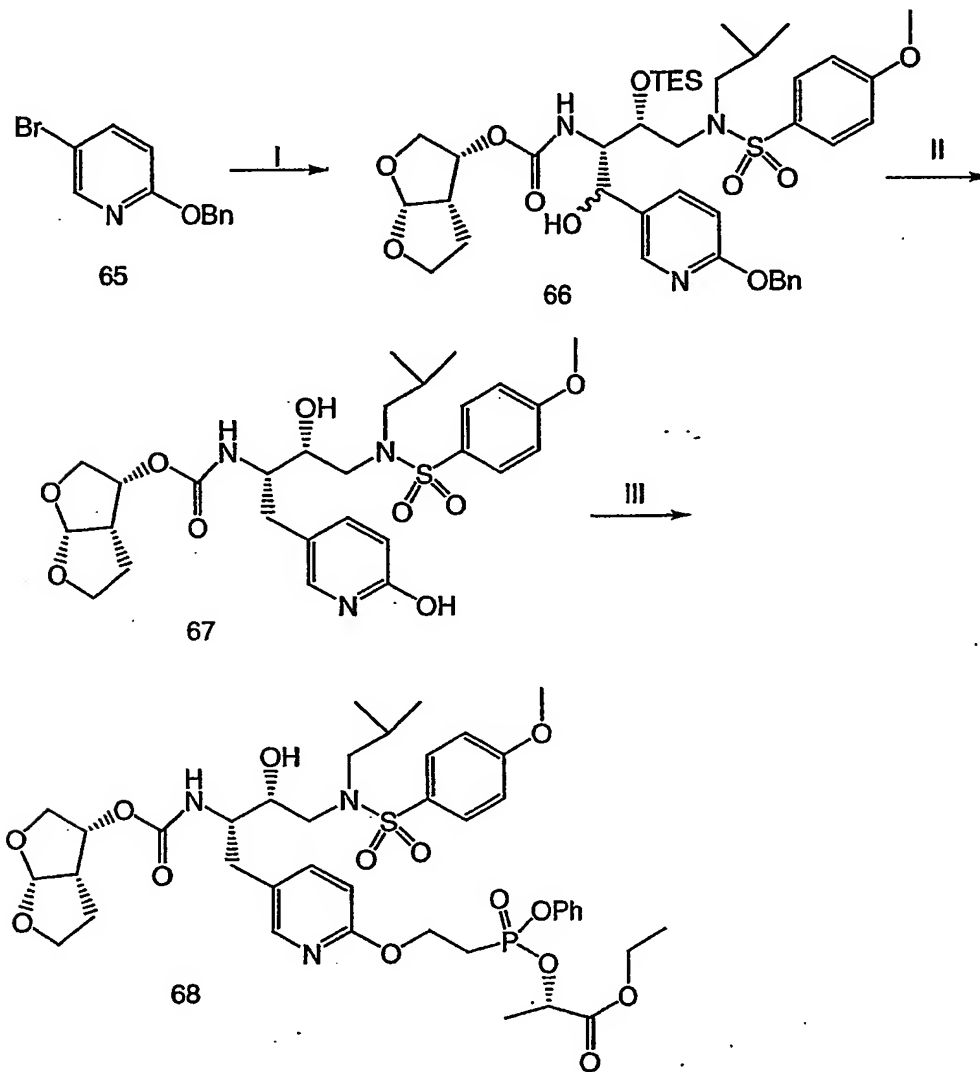
R = Me, Et, Pr, i-Pr; R<sub>1</sub> = H, Me, Et, i-Pr; Ar = phenyl, 2, 6-dimethylphenyl

I. a. CbzCl/NaOH; b. SOCl<sub>2</sub>/toluene/60 °C; c. ArOH/pyridine; II. a. NaOH/THF/H<sub>2</sub>O; b. HCl;  
 III. a. SOCl<sub>2</sub>/toluene/60 °C; b. alkyl lactate/pyridine; IV. H<sub>2</sub>/10%Pd-C/EtOAc/HOAc;  
 V. a. compound 6/MgSO<sub>4</sub>; b. HOAc/NaCNBH<sub>3</sub>

Aminomethylphosphonic acid 59 is protected as benzyl carbamate. The phosphonic acid is treated with thionyl chloride to generate dichloridate, which reacts with phenol or 2,6-dimethylphenol to give compound 60. Compound 60 is hydrolyzed with sodium hydroxide, followed by acidification to afford monoacid 61. Monoacid 61 is treated with thionyl chloride to generate monochloridate, which reacts with different alkyl (s)-lactates to form compound 62. Compound 62 is hydrogenated with 10%Pd-C in the presence of acetic acid to

give compound 63. Compound 63 reacts with aldehyde 6 in the presence of  $\text{MgSO}_4$  to form imine, which is reduced with sodium cyanoborohydride to generate compound 64.

#### Scheme 14



I.a. n-BuLi; b. compound 15; II.  $\text{H}_2/10\%\text{Pd-C}/\text{HOAc}$ ; IV.  $\text{PPh}_3/\text{DEAD}$

Compound 65 is prepared from 2-hydroxy-5-bromopyridine by alkylation. J. Med.

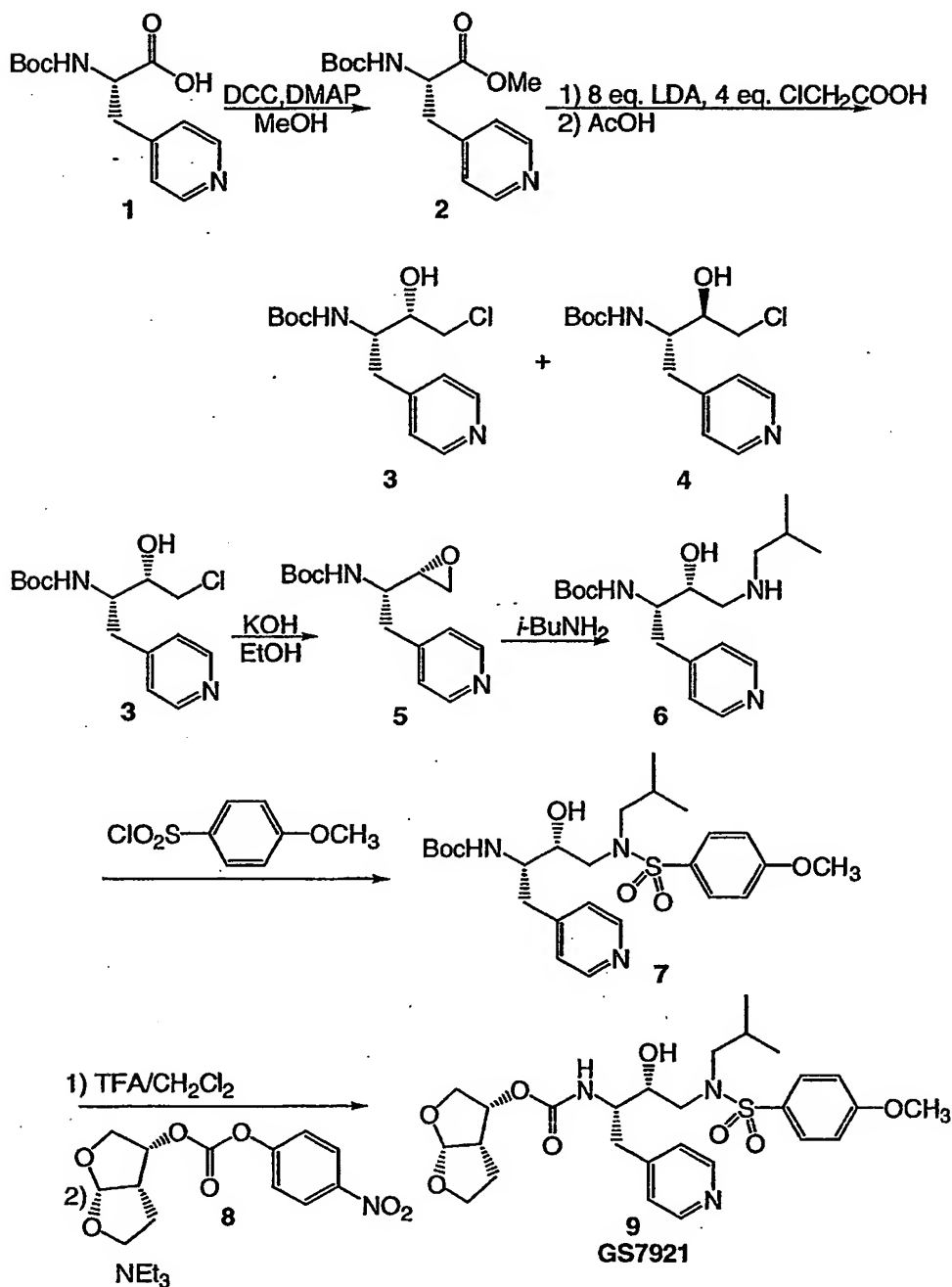
- 5 Chem. 1992, 35, 3525. Compound 65 is treated with n-Butyl lithium to generate aryl lithium, which reacts with aldehyde 15 to form compound 66. J. Med. Chem. 1994, 37, 3492.

Compound 66 is hydrogenated with 10% Pd-C in the presence of acetic acid to give compound 67. J. Med. Chem. 2000, 43, 721. Compound 68 is prepared from compound 67

with corresponding alcohol under Mitsunobu reaction conditions. Bioorg. Med. Chem. Lett., 1999, 9, 2747.

## Scheme 1

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Example 1

Methyl 2-(*S*)-(dimethylethoxycarbonylamino)-3-(4-pyridyl)propanoate (2): A solution of *N*-tert-Butoxycarbonyl-4-pyridylalanine (1, 9.854 g, 37 mmol, Peptech), 4-dimethylaminopyridine (4.52 g, 37 mmol, Aldrich), and dicyclohexylcarbodiimide (15.30 g, 74.2 mmol, Aldrich) in methanol (300 mL) was stirred at 0°C for 2 h and at room temperature for 12 h. After the solids were removed by filtration, the filtrate was concentrated under reduced pressure. More dicyclohexylurea was removed by repeated trituration of the concentrated residue in EtOAc followed by filtration. The residue was chromatographed on silica gel to afford the methyl ester 2 (9.088 g, 88%): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.53 (d, 2H, *J* = 5.7 Hz), 7.09 (d, 2H, *J* = 5.7 Hz), 5.04 (br, 1H), 4.64 (br, 1H), 3.74 (s, 3H), 3.16 (dd, 1H, *J* = 13.5 and 5.7 Hz), 3.02 (dd, 1H, *J* = 13.5 and 6.3 Hz), 1.42 (s, 9H); MS (ESI) 281 (M+H).

Example 2

1-Chloro-3-(*S*)-(dimethylethoxycarbonylamino)-4-(4-pyridyl)-2-(*S*)-butanol (3): A solution of diisopropylamine (37.3 mL, 266 mmol, Aldrich) in THF (135 mL) was stirred at -78°C as a solution of *n*-butyllithium (102 mL of 2.3 M solution and 18 mL of 1.4 M solution 260 mmol, Aldrich) in hexane was added. After 10 min, the cold bath was removed and stirred the solution for 10 min at the ambient temperature. The solution was cooled at -78°C again and stirred as a solution of chloroacetic acid (12.255 g, 130 mmol, Aldrich) in THF (50 mL) was added over 20 min. After the solution was stirred for 15 min, this dianion solution was transferred to a stirred solution of the methyl ester 2 (9.087 g, 32.4 mmol) in THF (100 mL) at 0°C over 15 min. The resulting yellow slurry was stirred at 0°C for 10 min and cooled at -78°C. A solution of acetic acid (29 mL, 507 mmol, Aldrich) in THF (29 mL) was added quickly to the slurry and the resulting slurry was stirred at -78°C for 30 min, at 0°C for 30 min, and at room temperature for 15 min. The resulting slurry was dissolved in saturated NaHCO<sub>3</sub> solution (750 mL) and EtOAc (500 mL). The separated aqueous layer was extracted with EtOAc (300 mL x 2) and the combined organic fractions were washed with water (750 mL x 2) and saturated NaCl solution (250 mL). The resulting solution was dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. A solution of the residue in THF (170 mL) and water (19 mL) was stirred at 0°C as NaBH<sub>4</sub> (3.375 g, 89.2 mmol, Aldrich) was added. After 30 min, the solution was evaporated under reduced pressure and the residue was dissolved in EtOAc, acidified with aqueous NaHSO<sub>4</sub>,

and then neutralized by adding saturated aqueous NaHCO<sub>3</sub> solution. The separated aqueous fraction was extracted with EtOAc (100 mL) and the combined organic fractions were washed with water (500 mL) and saturated NaCl solution (100 mL). The solution was dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The residue was chromatographed on silica gel to afford the chlorohydrin 3 and 4 (4.587 g, 47%) as a mixture of two diastereomers (3~4:1). The obtained mixture was recrystallized from EtOAc-hexane twice to obtain pure desired diastereomer 3 (2.444 g, 25%) as yellow crystals: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.53 (d, 2H, *J* = 5.7 Hz), 7.18 (d, 2H, *J* = 5.7 Hz), 4.58 (br, 1H), 3.94 (m, 1H), 3.87 (br, 1H), 3.75-3.54 (m, 2H), 3.05 (dd, 1H, *J* = 13.8 and 3.9 Hz), 2.90 (dd, 1H, *J* = 13.8 and 8.4 Hz), 1.36 (s, 9H); MS (ESI) 301 (M+H).

### Example 3

The epoxide 5: A solution of the chlorohydrin 3 (1.171 g, 3.89 mmol) in ethanol (39 mL) was stirred at room temperature as 0.71 M KOH in ethanol (6.6 mL) was added. After 1.5 h, the mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (60 mL) and water (60 mL). The separated aqueous fraction was extracted with EtOAc (60 mL) and the combined organic fractions were washed with saturated NaCl solution, dried (MgSO<sub>4</sub>), and concentrated under reduced pressure to obtain the epoxide (1.058 g, quantitative): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.52 (d, 2H, *J* = 6.0 Hz), 7.16 (d, 2H, *J* = 6.0 Hz), 4.57 (d, 1H, *J* = 7.8 Hz), 3.76 (br, 1H), 3.02-2.92 (m, 2H), 2.85-2.79 (m, 2H), 2.78-2.73 (m, 1H), 1.37 (s, 9H); MS (ESI) 265 (M+H).

### Example 4

The hydroxy-amine 6: A solution of the epoxide 5 obtained above and *i*-BuNH<sub>2</sub> (3.9 mL, 39.2 mmol, Aldrich) in 58 mL of *i*-PrOH was stirred at 65°C for 2 h and the solution was concentrated under reduced pressure. The residual *i*-PrOH was removed by dissolving the residue in toluene and concentration of the solution twice: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.51 (d, 2H, *J* = 6.0 Hz), 7.18 (d, 2H, *J* = 6.0 Hz), 4.70 (d, 1H, *J* = 9.6 Hz), 3.86 (br, 1H), 3.46 (q, 1H, *J* = 5.8 Hz), 3.06 (dd, 1H, *J* = 14.1 and 3.9 Hz), 2.79 (dd, 1H, *J* = 14.1 and 9.0 Hz), 2.76-2.63 (m, 3H), 2.43 (m, 2H, *J* = 6.9 Hz), 1.73 (m, 1H, *J* = 6.6 Hz), 1.36 (s, 9H), 0.93 (d, 3H, *J* = 6.6 Hz), 0.92 (d, 3H, *J* = 6.6 Hz); MS (ESI) 338 (M+H).



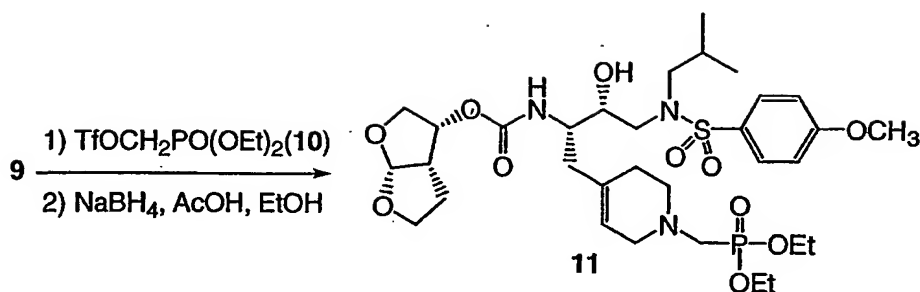
Example 5

The sulfoamide 7: A solution of the crude 6 and *p*-methoxybenzene sulfonyl chloride (890 mg, 4.31 mmol, Aldrich) in CH<sub>2</sub>Cl<sub>2</sub> (24 mL) was stirred at 0°C for 2 h and at room temperature for 13 h. The solution was washed with saturated NaHCO<sub>3</sub> solution and the aqueous washing was extracted with CH<sub>2</sub>Cl<sub>2</sub> (60 mL). After the combined organic fractions were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure, the residue was purified by chromatography on silica gel to obtain the sulfoamide 7 (1.484 g, 75%): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.51 (d, 2H, *J* = 5.7 Hz), 7.73 (d, 2H, *J* = 8.7 Hz), 7.21 (d, 2H, *J* = 5.7 Hz), 7.00 (d, 2H, *J* = 8.7 Hz), 4.68 (d, 1H, *J* = 8.1 Hz), 4.08 (br, 1H), 3.88 (s, 3H), 3.83 (br, 2H), 3.09 (d, 2H, *J* = 5.1 Hz), 3.06-2.80 (m, 4H), 1.85 (m, 1H, *J* = 7.0 Hz), 1.34 (s, 9H), 0.92 (d, 3H, *J* = 6.3 Hz), 0.89 (d, 3H, *J* = 6.6 Hz); MS (ESI) 508 (M+H).

Example 6

The bisfurancarbamate 9: A solution of the sulfoamide 7 (1.484 g, 2.92 mmol) and trifluoroacetic acid (6.8 mL, 88.3 mmol, Aldrich) in CH<sub>2</sub>Cl<sub>2</sub> (18 mL) was stirred at room temperature for 2 h. After the solution was evaporated under reduced pressure, the residue was dissolved in acetonitrile (10 mL) and toluene (10 mL), and evaporated to dryness twice to result crude amine as TFA salt. A solution of the crude amine, dimethylaminopyridine (72 mg, 0.59 mmol, Aldrich), diisopropylethylamine (2.55 mL, 14.6 mmol, Aldrich) in acetonitrile was stirred at 0°C as the bisfurancarboxylic acid 8 (907 mg, 3.07 mmol, obtained from Azar) was added in portion. The solution was stirred at 0°C for 1 h and at room temperature for 19 h, and concentrated under reduced pressure. The residue was dissolved in EtOAc (60 mL) and washed with saturated NaHCO<sub>3</sub> solution (60 mL). After the aqueous washing was extracted with EtOAc (60 mL), the combined organic fractions were washed with saturated NaHCO<sub>3</sub> (60 mL) and saturated NaCl solution (60 mL), dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to obtain the carbamate 9 (1.452 g, 88%): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.50 (d, 2H, *J* = 5.7 Hz), 7.72 (d, 2H, *J* = 8.7 Hz), 7.19 (d, 2H, *J* = 5.7 Hz), 7.01 (d, 2H, *J* = 8.7 Hz), 5.65 (d, 1H, *J* = 5.1 Hz), 5.12 (d, 1H, *J* = 9.3 Hz), 5.02 (q, 1H, *J* = 6.7 Hz), 4.01-3.77 (m, 4H), 3.88 (s, 3H), 3.76-3.63 (m, 2H), 3.18-2.76 (m, 7H), 1.95-1.77 (m, 1H), 1.77-1.56 (m, 2H), 1.56-1.41 (m, 1H), 0.94 (d, 3H, *J* = 6.6 Hz), 0.90 (d, 3H, *J* = 6.9 Hz); MS (ESI) 564 (M+H).

Scheme 2

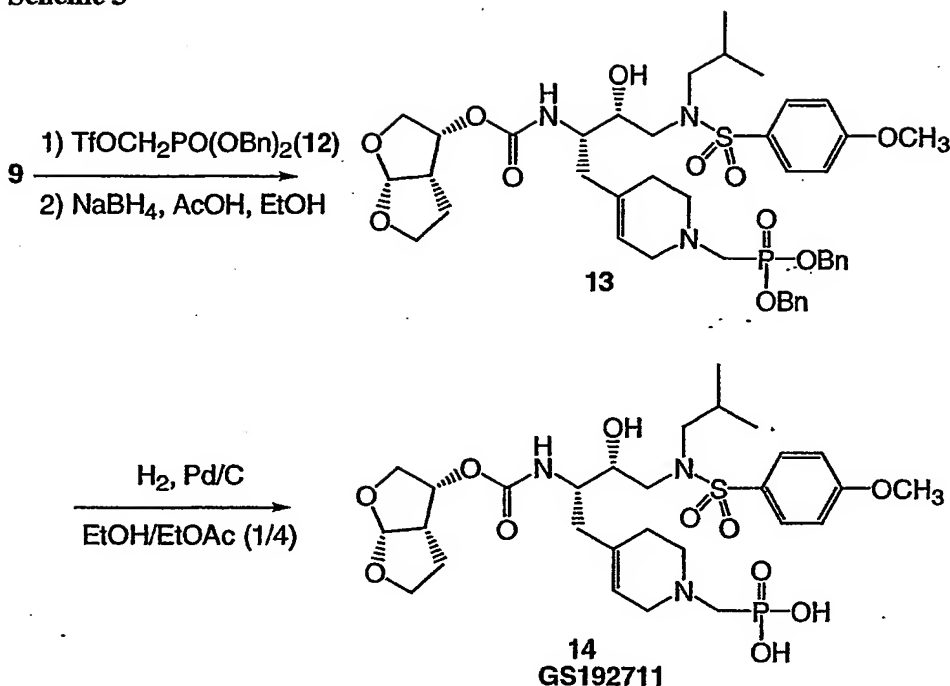


GS192710

Example 7

The tetrahydropyridine-diethyl phosphonate 11: A solution of the pyridine 9 (10.4 mg, 0.018 mmol) and the triflate 10 (8.1 mg, 0.027 mmol, in acetone- $d_6$  (0.75 mL) was stored at room temperature for 9 h and the solution was concentrated under reduced pressure:  $^{31}\text{P}$  NMR (acetone- $d_3$ )  $\delta$  14.7; MS (ESI) 714 ( $\text{M}^+$ ). The concentrated crude pyridinium salt was dissolved in ethanol (2 mL) and stirred at room temperature as  $\text{NaBH}_4$  (~10 mg, Aldrich) was added occasionally over 4 h. To the mixture was added a solution of acetic acid (0.6 mL, Aldrich) in ethanol (3 mL) until the pH of the mixture became 3~4. More  $\text{NaBH}_4$  and acetic acid were added until the reaction was completed. The mixture was carefully concentrated under reduced pressure and the residue was dissolved in saturated  $\text{NaHCO}_3$  solution (10 mL). The product was extracted using  $\text{EtOAc}$  (10 mL x 3) and washed with saturated  $\text{NaCl}$  solution, dried ( $\text{MgSO}_4$ ), and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to obtain the product 11 (8.5 mg, 64%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.73 (d, 2H,  $J = 8.7$  Hz), 7.00 (d, 2H,  $J = 8.7$  Hz), 5.71 (d, 1H,  $J = 5.1$  Hz), 5.41 (br, 1H), 5.15-5.08 (m, 1H), 5.00 (br, 1H), 4.14 (dq, 4H,  $J = 7.2$  Hz), 4.06-3.94 (m, 2H), 3.88 (s, 3H), 3.92-3.80 (m, 2H), 3.75 (dd, 1H,  $J = 9.6$  and 6.6 Hz), 3.79-3.61 (m, 1H), 3.24-2.94 (m, 6H), 2.85 (d, 2H,  $J = 11.7$  Hz), 2.88-2.76 (m, 2H), 2.75-2.63 (m, 1H), 2.38-2.29 (m, 1H), 2.24-2.2.12 (m, 2H), 2.12-1.78 (m, 4H), 1.30 (t, 6H,  $J = 7.1$  Hz), 0.94 (d, 3H,  $J = 6.6$  Hz), 0.91 (d, 3H,  $J = 6.3$  Hz);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  24.6; MS (ESI) 740 ( $\text{M}+\text{Na}$ ).

## Scheme 3



## Example 8

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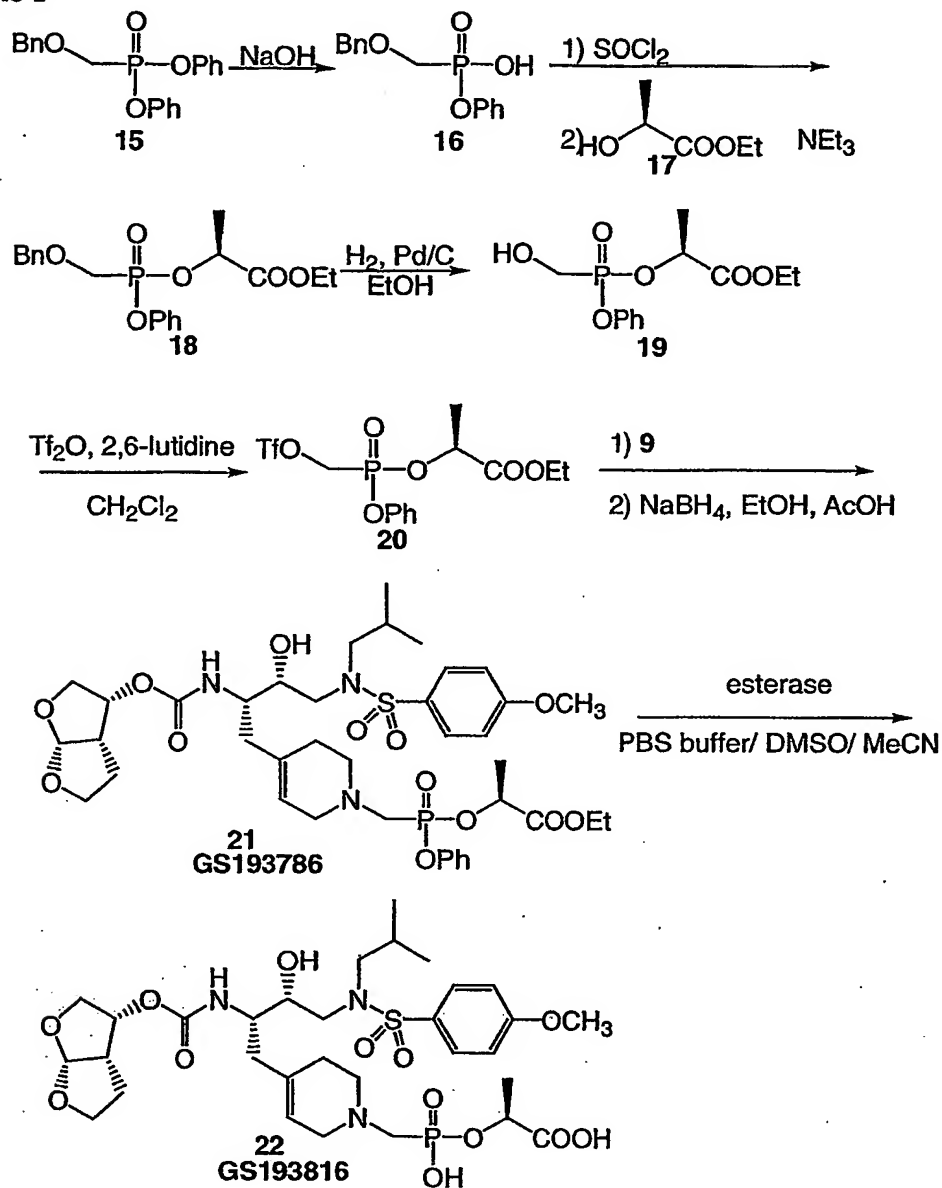
The tetrahydropyridine-dibenzyl phosphonate 13: The compound 13 was obtained by the same procedure as described for compound 11 using the pyridine 9 (10.0 mg, 0.018 mmol) and the triflate 12 (9.4 mg, 0.022 mmol). The product 13 was purified by preparative TLC to afford the dibenzyl phosphonate 13 (8.8 mg, 59%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.73 (d, 2H,  $J = 8.7$  Hz), 7.35 (s, 10H), 7.00 (d, 2H,  $J = 8.7$  Hz), 5.65 (d, 1H,  $J = 5.1$  Hz), 5.39 (br, 1H), 5.15-4.92 (m, 6H), 4.03-3.77 (m, 6H), 3.77-3.62 (m, 2H), 3.56 (br, 1H), 3.24-2.62 (m, 9H), 2.32 (d, 1H,  $J = 13.5$  Hz), 2.24-1.75 (m, 6H), 0.94 (d, 3H,  $J = 6.6$  Hz), 0.89 (d, 3H,  $J = 6.3$  Hz);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  25.5; MS (ESI) 842 (M+H).

## 15 Example 9

The phosphonic acid 14: A mixture of the dibenzyl phosphonate 13 (8.8 mg, 0.011 mmol) and 10% Pd/C in EtOAc (2 mL) and EtOH (0.5 mL) was stirred under  $\text{H}_2$  atmosphere for 10 h at room temperature. After the mixture was filtered through celite, the filtrate was concentrated to dryness to afford the product 14 (6.7 mg, quantitative):  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.76 (d, 2H,  $J = 9.0$  Hz), 7.10 (d, 2H,  $J = 9.0$  Hz), 5.68 (d, 1H,  $J = 5.1$  Hz), 5.49 (br, 1H), 5.11 (m, 1H), 3.90 (s, 3H), 4.04-3.38 (m, 10H), 3.22 (d, 2H,  $J = 12.9$  Hz), 3.18-3.00 (m, 2H),

2.89-2.75 (m, 2H), 2.68-2.30 (m, 3H), 2.21-1.80 (m, 4H), 0.92 (d, 3H,  $J = 6.3$  Hz), 0.85 (d, 3H,  $J = 6.3$  Hz);  $^{31}\text{P}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  6.29; MS (ESI) 662 ( $\text{M}+\text{H}$ ).

Scheme 4



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Example 10

Diphenyl benzyloxymethylphosphonate 15: To a solution of diphenylphosphite (46.8 g, 200.  
10 mmol, Aldrich) in acetonitrile (400 mL) (at ambient temperature) was added potassium carbonate (55.2 g, 400 mmol) followed by the slow addition of benzyl chloromethyl ether (42

mL, 300 mmol, about 60%, Fluka). The mixture was stirred overnight, and was concentrated under reduced pressure. The residue was dissolved in EtOAc, washed with water, saturated NaCl, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated. The crude product was chromatographed on silica gel to afford the benzylether (6.8 g, 9.6%) as a colorless liquid.

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#### Example 11

Monoacid 16: To a solution of diphenyl benzyloxymethylphosphonate 15 (6.8 g, 19.1 mmol) in THF (100 mL) at room temperature was added 1N NaOH in water (21 mL, 21 mmol). The solution was stirred 3 h. The THF was evaporated under reduced pressure and water (100 mL) was added. The aqueous solution was cooled to 0°C, neutralized to pH 7 with 3N HCl and washed with EtOAc. The aqueous solution was again cooled to 0°C, acidified with 3N HCl to pH 1, saturated with sodium chloride, and extracted with EtOAc. The organic layer was washed with brine and dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated, then co-evaporated with toluene to yield the monoacid (4.0 g, 75%) as a colorless liquid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.28-7.09 (m, 10H), 4.61 (s, 2H), 3.81 (d, 2H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 20.8.

#### Example 12

Ethyl lactate phosphonate 18: To a solution of monoacid 16 (2.18 g, 7.86 mmol) in anhydrous acetonitrile (50 mL) under a nitrogen atmosphere was slowly added thionyl chloride (5.7 mL, 78 mmol). The solution was stirred in a 70°C oil bath for three hours, cooled to room temperature and concentrated. The residue was dissolved in anhydrous dichloromethane (50 mL), and this solution cooled to 0°C and stirred under a nitrogen atmosphere. To the stirring solution was added ethyl (S)-(-)-lactate (2.66 mL, 23.5 mmol) and triethylamine (4.28 mL, 31.4 mmol). The solution was warmed to room temperature and allowed to stir for one hour. The solution was diluted with ethyl acetate, washed with water, brine, citric acid and brine again, dried (MgSO<sub>4</sub>), filtered through Celite, concentrated under reduced pressure and chromatographed on silica gel using 30% ethylacetate in hexane. The two diastereomers were pooled together. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.40-7.16 (m, 20H), 5.18-5.13 (m, 2H), 4.73 (s, 2H), 4.66 (d, 2H), 4.28-4.11 (m, 5H), 4.05 (d, 2H), 3.95 (d, 2H), 1.62 (d, 3H), 1.46 (d, 3H), 1.30-1.18 (m, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 19.6, 17.7.

Example 13

Ethyl lactate phosphonate with free alcohol 19: Ethyl lactate phosphonate 18 was dissolved in EtOH (50mL) and under a nitrogen atmosphere 10% Pd-C (approximately 20 wt %) was added. The nitrogen atmosphere was replaced with hydrogen (1atm) and the suspension stirred for two hours. 10% Pd-C was again added (20 wt %) and the suspension stirred five hours longer. Celite was added, the reaction mixture was filtered through Celite and the filtrate was concentrated to afford 1.61 g (71% from monoacid 16) of the alcohol as a colorless liquid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.40-7.16 (m, 10H), 5.16-5.03 (m, 2H), 4.36-4.00 (m, 8H), 1.62 (d, 3H), 1.46 (d, 3H), 1.30-1.22 (m, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  22.3, 20.0.

Example 14

Triflate 20: To a solution of ethyl lactate phosphonate with free alcohol 19 (800 mg, 2.79 mmol) in anhydrous dichloromethane (45 mL) chilled to  $-40^\circ\text{C}$  under a nitrogen atmosphere was added triflic anhydride (0.516 mL, 3.07 mmol) and 2-6 lutidine (0.390 mL, 3.34 mmol). The solution was stirred for 3 hr, then warmed to  $-20^\circ\text{C}$  and stirred one hour longer. 0.1 equivalents of triflic anhydride and 2-6 lutidine were then added and stirring was resumed for 90 minutes more. The reaction mixture was diluted with ice-cold dichloromethane, washed with ice-cold water, washed with ice-cold brine and the organic layer was dried ( $\text{MgSO}_4$ ) and filtered. The filtrate was concentrated and chromatographed on silica gel using 30% EtOAc in hexane as eluent to afford 602 mg (51%) of the triflate diastereomers as a slightly pink, transparent liquid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.45-7.31 (m, 4H), 7.31-7.19 (m, 6H), 5.15-4.75 (m, 6H), 4.32-4.10 (4H), 1.62 (d, 3H), 1.50 (d, 3H), 1.30-1.22 (m, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  10.3, 8.3.

Example 15

The tetrahydropyridine-prodrug 21: A solution of the pyridine 9 (11.1 mg, 0.020 mmol) and the triflate 20 (11.4 mg, 0.027 mmol) in acetone- $d_6$  (0.67 mL, Aldrich) was stored at room temperature for 7 h and the solution was concentrated under reduced pressure:  $^{31}\text{P}$  NMR (acetone- $d_6$ )  $\delta$  11.7, 10.9; MS (ESI) 838 (M+H). The concentrated crude pyridinium salt was dissolved in ethanol (1 mL) and added 2~3 drops of a solution of acetic acid (0.6 mL, Aldrich) in ethanol (3 mL). The solution was stirred at  $0^\circ\text{C}$  as  $\text{NaBH}_4$  (7~8 mg, Aldrich) was

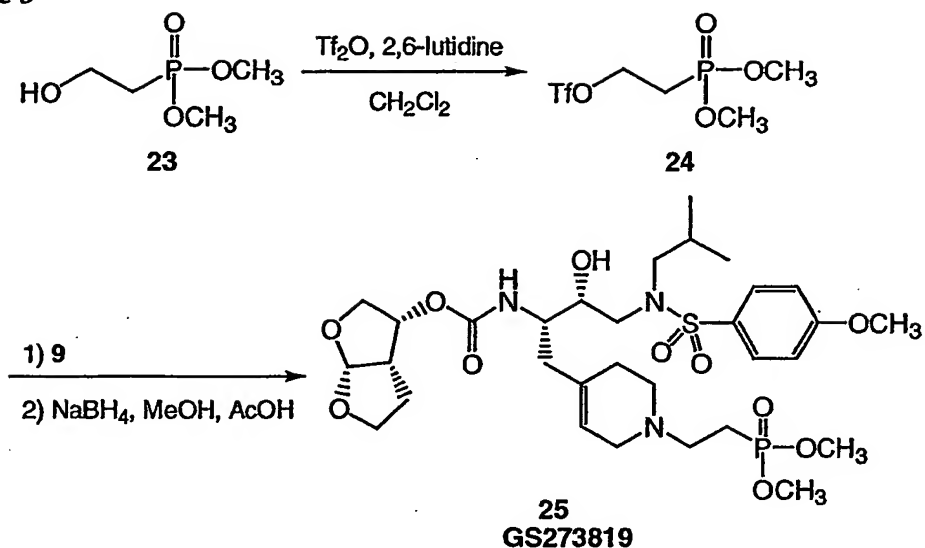
added. More acetic acid solution was added to adjust pH 3~4 of the reaction mixture. Additions of NaBH<sub>4</sub> and the acetic acid solution were repeated until the reaction was completed. The mixture was carefully concentrated under reduced pressure and the residue was purified by chromatography on C18 reverse phase column material followed by

5 preparative TLC using C18 reverse phase plate to obtain the prodrug 21 (13.6 mg, 70%) as a 2:3 mixture of two diastereomers: <sup>1</sup>H NMR (CD<sub>3</sub>CN) δ 7.78 (d, 2H, *J* = 9.0 Hz), 7.48-7.42 (m, 2H), 7.35-7.27 (m, 3H), 7.10 (d, 2H, *J* = 9.0 Hz), 5.86 (m, 1H), 5.60 (m, 1H), 5.48 (br, 1H), 5.14-5.03 (m, 2H), 4.29-4.13 (m, 2H), 3.89 (s, 3H), 3.97-3.32 (m, 12H), 3.29 (br, 0.4H), 3.24 (br, 0.6H), 3.02-2.82 (m, 4H), 2.64-2.26 (m, 3H), 2.26-2.08 (m, 1H), 1.94-1.76 (m, 3H),  
10 1.57 (d, 1.8H, *J* = 6.9 Hz), 1.46 (d, 1.2H, *J* = 6.9 Hz), 1.28 (d, 1.2H, *J* = 6.9 Hz), 1.21 (d, 1.8H, *J* = 7.2 Hz), 0.92-0.88 (m, 6H); <sup>31</sup>P NMR (CD<sub>3</sub>CN) δ 14.4 (0.4P), 13.7 (0.6P); MS (ESI) 838 (M+H).

#### Example 16

15 Metabolite 22: To a solution of the prodrug 21 (10.3 mg, 0.011 mmol) in DMSO (0.1 mL) and acetonitrile (0.2 mL) was added 0.1 M PBS buffer (3 mL) mixed thoroughly to result a suspension. To the suspension was added porcine liver esterase suspension (0.05 mL, EC3.1.1.1, Sigma). After the suspension was stored in 37°C for 1.5 h, the mixture was  
20 centrifuged and the supernatant was taken. The product was purified by HPLC and the collected fraction was lyophilized to result the product 22 as trifluoroacetic acid salt (7.9 mg, 86%): <sup>1</sup>H NMR (D<sub>2</sub>O) δ 7.70 (d, 1H), 7.05 (d, 2H), 5.66 (d, 1H), 5.40 (br, 1H), 5.02 (br, 1H), 4.70 (br, 1H), 3.99-3.89 (m, 2H), 3.81 (s, 3H), 3.83-3.50 (m, 8H), 3.34-2.80 (m, 7H), 2.50-2.18 (m, 3H), 2.03 (m, 1H), 1.92-1.70 (m, 3H), 1.39 (d, 3H), 0.94 (d, 3H), 0.93 (d, 3H);  
25 <sup>31</sup>P NMR (D<sub>2</sub>O) δ 9.0, 8.8; MS (ESI) 734 (M+H).

Scheme 5

Example 17

5

Triflate 24: Triflate **24** was prepared analogously to triflate **20**, except that dimethylhydroxyethylphosphonate **23** (Aldrich) was substituted for ethyl lactate phosphonate with free alcohol **19**.

10 Example 18

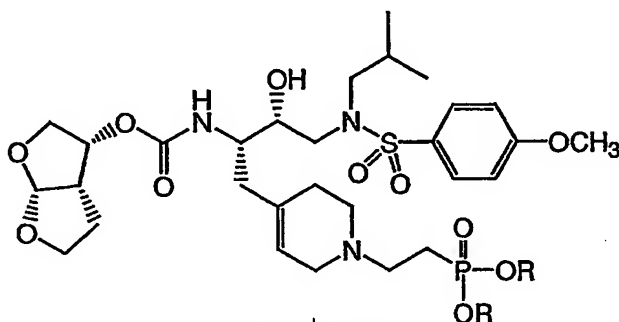
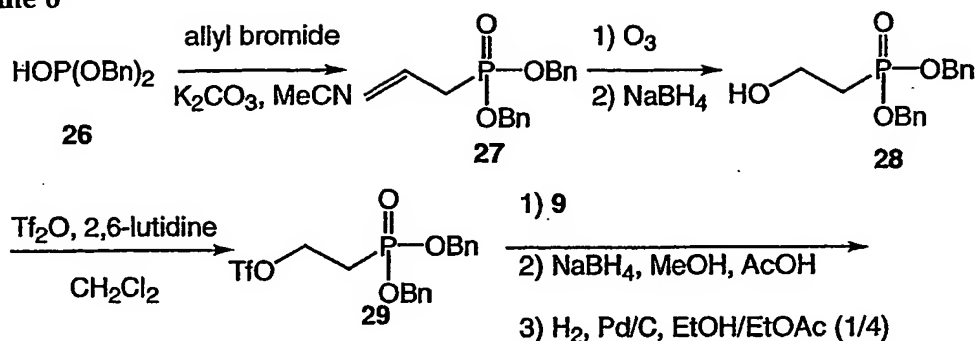
Tetrahydropyridine 25: Tetrahydropyridine **25** was prepared analogously to tetrahydropyridine **30**, except that triflate **24** was substituted for triflate **29**.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71 (d, 2H), 7.01 (d, 2H), 5.71 (d, 2H), 5.43 (bs, 1H), 5.07-4.87 (m, 1H), 4.16-3.46 (m, 13H), 3.34-3.18 (m, 3H), 3.16-2.80 (m, 5H), 2.52-1.80 (m, 12H), 1.28-1.04 (m, 3H+ $\text{H}_2\text{O}$  peak), 0.98-0.68 (m, 6H).

15



Scheme 6



30: R = Bn (GS173848)  
 31: R = H (GS173850)

### 5 Example 19

Dibenzy phosphonate with double bond 27: To a stirring solution of allyl bromide (4.15 g, 34 mmol, Aldrich) and dibenzylphosphite (6 g, 23 mmol, Aldrich) in acetonitrile (25 mL) was added potassium carbonate (6.3 g, 46 mmol, powder 325 mesh Aldrich) to create a suspension, which was heated to 65°C and stirred for 72 hours. The suspension was cooled to room temperature, diluted with ethyl acetate, filtered, and the filtrate was washed with water, then brine, dried (MgSO<sub>4</sub>), concentrated and used directly in the next step.

### Example 20

Dibenzyldihydroxyethylphosphonate 28: Dibenzy phosphonate with double bond 27 was dissolved in methanol (50mL), chilled to -78°C, stirred, and subjected to ozone by bubbling ozone into the solution for three hours until the solution turned pale blue. The ozone flow was stopped and oxygen bubbling was done for 15 minutes until the solution became colorless. Sodium borohydride (5 g, excess) was added slowly portionwise. After the evolution of gas subsided the solution was allowed to warm to room temperature, concentrated, diluted with ethyl acetate, made acidic with acetic acid and water and

partitioned. The ethyl acetate layer was washed with water, then brine and dried ( $\text{MgSO}_4$ ), filtered, concentrated and chromatographed on silica gel eluting with a gradient of eluent from 50% ethyl acetate in hexane to 100% ethyl acetate, affording 2.76 g of the desired product.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.36 (m, 10H), 5.16–4.95 (m, 4H), 3.94–3.80 (dt, 2H), 2.13–2.01 (dt, 2H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  31.6.

#### Example 21

Dibenzyl phosphonate 30: A solution of the alcohol 28 (53.3 mg, 0.174 mmol) and 2,6-lutidine (0.025 mL, 0.215 mmol, Aldrich) in  $\text{CH}_2\text{Cl}_2$  (1 mL) was stirred at  $-45^\circ\text{C}$  as trifluoromethanesulfonic anhydride (0.029 mL, 0.172 mmol, Aldrich) was added. The solution was stirred for 1 h at  $-45^\circ\text{C}$  and evaporated under reduced pressure to obtain the crude triflate 29.

A solution of the crude triflate 29, 2,6-lutidine (0.025 mL, 0.215 mmol, Aldrich), and the pyridine 9 in acetone- $d_6$  (1.5 mL, Aldrich) was stored at room temperature for 2 h. The solution was concentrated under reduced pressure to obtain crude pyridinium product:  $^{31}\text{P}$  NMR (acetone- $d_6$ )  $\delta$  25.8; MS (ESI) 852 ( $\text{M}^+$ ).

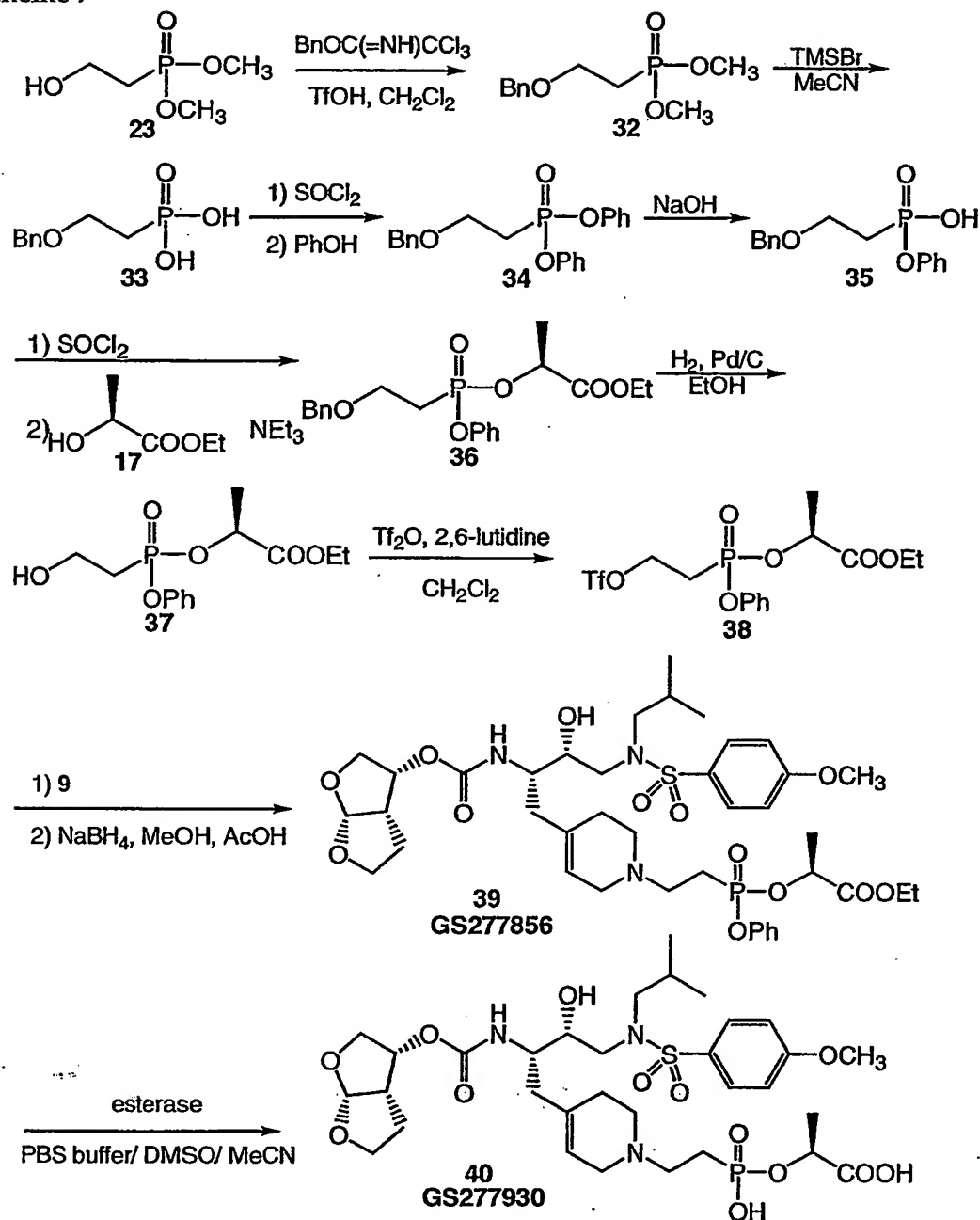
To a solution of the crude pyridinium salt in ethanol (2 mL) was added 7–8 drops of a solution of acetic acid (0.4 mL, Aldrich) in ethanol (2 mL). The solution was stirred at  $0^\circ\text{C}$  as  $\text{NaBH}_4$  (7–8 mg) was added. The solution was maintained to be pH 3–4 by adding the acetic acid solution. More  $\text{NaBH}_4$  and the acetic acid were added until the reduction was completed. After 4 h, the mixture was concentrated and the remaining residue was dissolved in saturated  $\text{NaHCO}_3$  (10 mL). The product was extracted with EtOAc (10 mL x 3), dried ( $\text{MgSO}_4$ ), and concentrated under reduced pressure. The residue was purified by repeated chromatography on silica gel followed by HPLC purification. Lyophilization of the collected fraction resulted the product 30 (13.5 mg, 26%) as trifluoroacetic acid salt:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.72 (d, 2H,  $J = 8.7$  Hz), 7.36 (br, 10H), 7.00 (d, 2H,  $J = 8.7$  Hz), 5.69 (d, 1H,  $J = 5.1$  Hz), 5.41 (br, 1H), 5.13–4.93 (m, 6H), 4.05–2.5 (m, 19H), 3.88 (s, 3H), 2.5–1.9 (m, 5H), 1.90–1.74 (m, 2H), 0.88 (d, 6H,  $J = 6.1$  Hz);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  25.8; MS (ESI) 856 ( $\text{M}+\text{H}$ ).

#### Example 22

Phosphonic acid 31: A mixture of the dibenzyl phosphonate 30 (9.0 mg, 0.009 mmol) and 10% Pd/C (5.2 mg, Aldrich) in EtOAc (2 mL) and ethanol (0.5 mL) was stirred under  $\text{H}_2$  atmosphere for 3 h at room temperature. After the mixture was filtered through celite, a drop

of trifluoroacetic acid (Aldrich) was added to the filtrate and the filtrate was concentrated to dryness to afford the product 31 (6.3 mg, 86%):  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.76 (d, 2H,  $J = 9.0$  Hz), 7.11 (d, 2H,  $J = 9.0$  Hz), 5.69 (d, 1H,  $J = 5.1$  Hz), 5.54 (br, 1H), 5.09 (br, 1H), 4.05-3.84 (m, 4H), 3.89 (s, 3H), 3.84-3.38 (m, 9H), 3.07 (dd, 2H,  $J = 13.5$  and  $8.4$  Hz), 2.9-2.31 (m, 5H), 2.31-1.83 (m, 6H), 0.92 (d, 3H,  $J = 6.3$  Hz), 0.85 (d, 3H,  $J = 6.9$  Hz);  $^{31}\text{P}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  21.6; MS (ESI) 676 (M+H).

Scheme 7

5 Example 23

**Benzylether 32:** A solution of dimethyl hydroxyethylphosphonate (5.0 g, 32.5 mmol, Across) and benzyl 2,2,2-trichloroacetimidate (97.24 mL, 39.0 mmol, Aldrich) in  $\text{CH}_2\text{Cl}_2$  (100 mL) at  $0^\circ\text{C}$  under a nitrogen atmosphere was treated with trifluoromethanesulfonic acid (0.40 mL). Stirring was performed for three hours at  $0^\circ\text{C}$  and the reaction was then allowed to warm to

room temperature while stirring continued. The reaction continued for 15 hours, and the reaction mixture was then diluted with dichloromethane, washed with saturated sodium bicarbonate, washed with brine, dried ( $\text{MgSO}_4$ ), concentrated under reduced pressure and chromatographed on silica gel eluting with a gradient of eluent from 60% EtOAc in hexane to 100% EtOAc to afford 4.5 g, (57%) of the benzyl ether as a colorless liquid.  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  31.5.

#### Example 24

Diacid 33: A solution of benzylether 32 (4.5 g, 18.4 mmol) was dissolved in anhydrous acetonitrile (100mL), chilled to  $0^\circ\text{C}$  under a nitrogen atmosphere and treated with TMS bromide (9.73 mL, 74mmol). The reaction mixture was warmed to room temperature and after 15 hours of stirring was concentrated repeatedly with MeOH/water to afford the diacid, which was used directly in the next step.  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  31.9.

#### Example 25

Diphenylphosphonate 34 : Diacid 33 (6.0 g, 27 mmol) was dissolved in toluene and concentrated under reduced pressure three times, dissolved in anhydrous acetonitrile, stirred under a nitrogen atmosphere, and treated with thionyl chloride (20 mL, 270 mmol) by slow addition. The solution was heated to  $70^\circ\text{C}$  for two hours, then cooled to room temperature, concentrated and dissolved in anhydrous dichloromethane, chilled to  $-78^\circ\text{C}$  and treated with phenol (15 g, 162 mmol) and triethylamine (37 mL, 270 mmol). The reaction mixture was warmed to room temperature and stirred for 15 hours, and was then diluted with ice cold dichloromethane, washed with ice cold 1 N. NaOH, washed with ice cold water, dried ( $\text{MgSO}_4$ ), and concentrated under reduced pressure. The resulting residue was used directly in the next step.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.40-7.16 (d, 15H), 4.55 (s, 2H), 3.98-3.84 (m, 2H), 2.55-2.41 (m, 2H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  22.1.

#### Example 26

Mono acid 35: Monoacid 35 was prepared using conditions analogous to those used to prepare monoacid 16, except that diphenylphosphonate 34 was substituted for benzylether 15.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.38-7.16 (d, 10H), 4.55 (s, 2H), 3.82-3.60 (m, 3H), 2.33-2.21 (m, 2H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  29.0.

Example 27

Ethyl lactate phosphonate 36: Ethyl lactate phosphonate 36 was prepared analogously to ethyl lactate phosphonate 18 except monoacid 35 was substituted for monoacid 16. <sup>31</sup>P NMR  
5 (CDCl<sub>3</sub>) δ 27.0, 25.6.

Example 28

Ethyl lactate phosphonate with free alcohol 37: Ethyl lactate phosphonate with free alcohol 37 was prepared analogously to ethyl lactate phosphonate with free alcohol 19 except that  
10 ethyl lactate phosphonate 36 was substituted for ethyl lactate phosphonate 18. <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 28.9, 26.8.

Example 29

Triflate 38: A solution of the alcohol 37 (663 mg, 2.19 mmol) and 2,6-lutidine (0.385 mL, 3.31 mmol, Aldrich) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was stirred at -45°C as trifluoromethanesulfonic  
15 anhydride (0.48 mL, 2.85 mmol, Aldrich) was added. The solution was stirred for 1.5 h at -45°C, diluted with ice-cold water (50 mL), and extracted with EtOAc (30 mL x 2). The combined extracts were washed with ice cold water (50 mL), dried (MgSO<sub>4</sub>), and concentrated under reduced pressure to obtain a crude mixture of two diastereomers (910 mg,  
20 96%, 1:3 ratio): <sup>1</sup>H NMR (acetone-d<sub>6</sub>) δ 7.48-7.37 (m, 2H), 7.37-7.18 (m, 3H), 5.2-4.95 (m, 3H), 4.3-4.02 (m, 2H), 3.38-3.0 (m, 1H), 3.0-2.7 (m, 2H), 2.1-1.9 (m, 1H), 1.52 (d, 1H), 1.4 (d, 2H), 1.4-1.1 (m, 3H); <sup>31</sup>P NMR (acetone-d<sub>6</sub>) δ 21.8 (0.75P), 20.5 (0.25P).

Example 30

The prodrug 39: A solution of the crude triflate 38 (499 mg, 1.15 mmol) and the pyridine 9 (494 mg, 0.877 mmol) in acetone (5 mL) was stirred at room temperature for 16.5 h. The solution was concentrated under reduced pressure to obtain the crude pyridinium salt.  
To a solution of the crude pyridinium salt in ethanol (10 mL) was added 5 drops of a solution of acetic acid (1 mL) in ethanol (5 mL). The solution was stirred at 0°C as NaBH<sub>4</sub> (~10 mg,  
30 Aldrich) was added. The solution was maintained to be pH 3-4 by adding the acetic acid solution. More NaBH<sub>4</sub> and the acetic acid were added until the reduction was completed. After 5.5 h, the mixture was concentrated under reduced pressure and the remaining residue was dissolved in ice-cold saturated NaHCO<sub>3</sub> (50 mL). The product was extracted with ice-

cold EtOAc (30 mL x 2) and the combined extracts were washed with 50% saturated NaHCO<sub>3</sub> (50 mL), dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The residue was purified by a chromatography on silica gel followed by a chromatography on C18 reverse phase column material. Lyophilization of the collected fraction resulted the product

5 39 mixture (376 mg, 50%, ~2.5:1 ratio) as trifluoroacetic acid salt: <sup>1</sup>H NMR (CD<sub>3</sub>CN+TFA) δ 7.78 (d, 2H, *J* = 8.7 Hz), 7.52-7.42 (m, 2H); 7.37-7.22 (m 3H), 7.10 (d, 2H, *J* = 8.7 Hz), 5.78 (d, 1H, *J* = 9.0 Hz), 5.64 (m, 1H), 5.50 (br, 1H), 5.08 (m, 2H), 4.31-4.12 (m, 2H), 4.04-3.42 (m, 11H), 3.90 (s, 3H), 3.29 (m, 2H), 3.23-3.16 (m, 1H), 3.08-2.78 (m, 6H), 2.76-2.27 (m, 5H), 2.23-2.11 (m, 1H), 2.08-1.77 (m, 3H), 1.58 (d, 0.9H, *J* = 7.2 Hz), 1.45 (d, 2.1H, *J* =

10 6.6 Hz), 1.32-1.20 (m, 3H), 0.95 - 0.84 (m, 6H); <sup>31</sup>P NMR (CD<sub>3</sub>CN+TFA) δ 24.1 and 23.8, 22.2 and 22.1; MS (ESI) 852 (M+H).

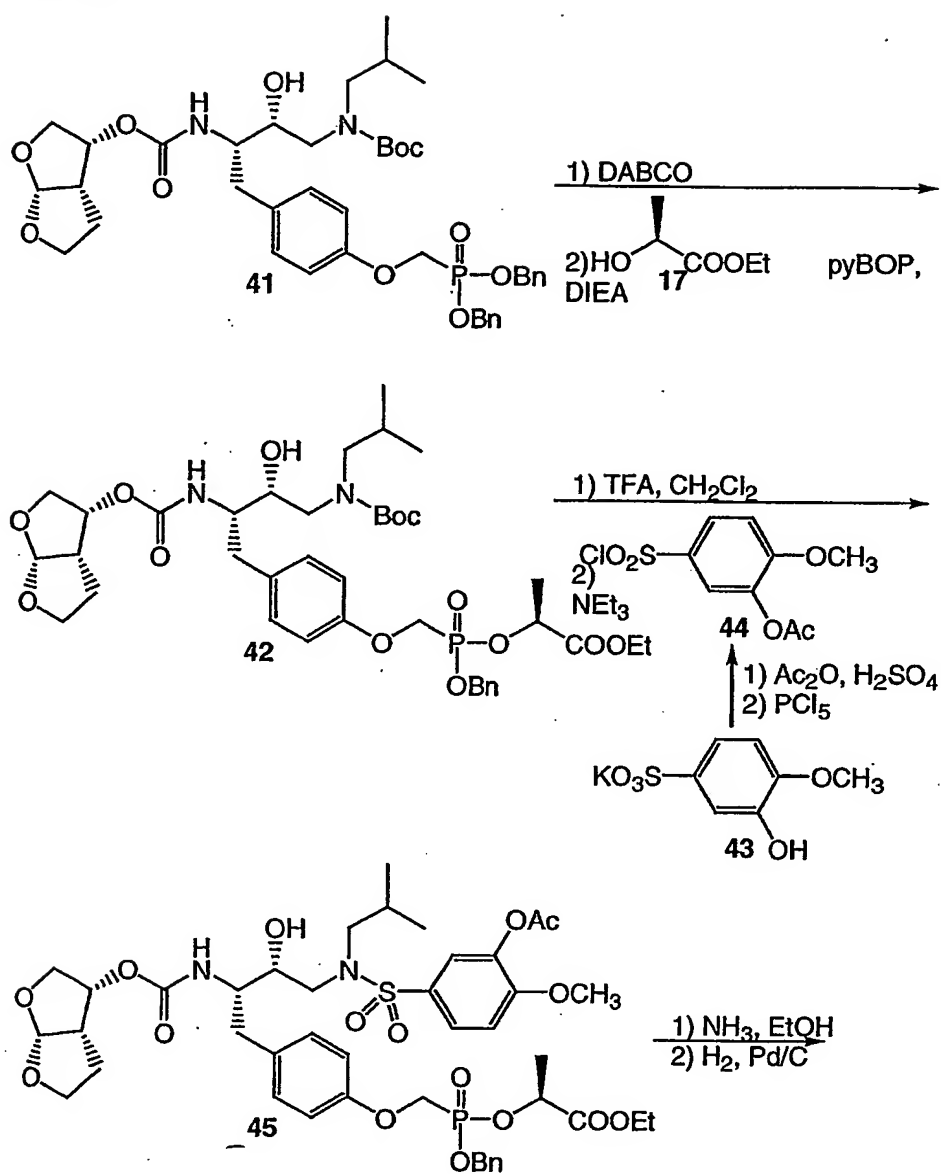
### Example 31

Metabolite 40: To a solution of the prodrug 39 (35.4 mg, 0.037 mmol) in DMSO (0.35 mL)

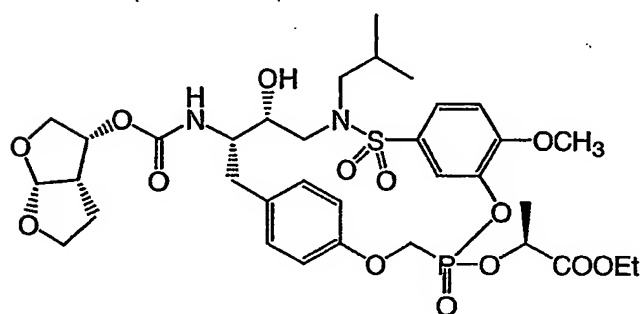
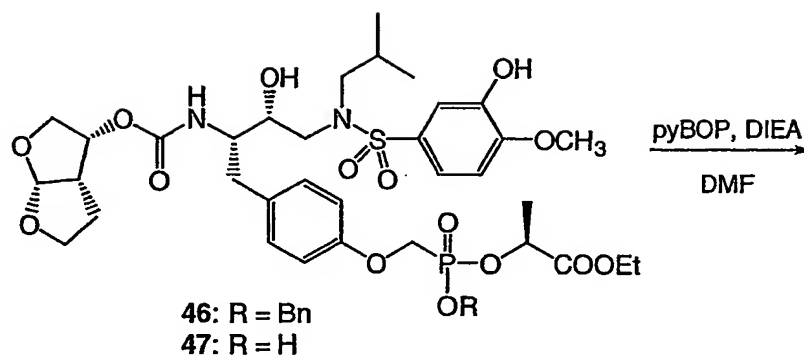
15 and acetonitrile (0.70 mL) was added 0.1 M PBS buffer (10.5 mL) mixed thoroughly to result a suspension. To the suspension was added porcine liver esterase suspension (0.175 mL, EC3.1.1.1, Sigma). After the suspension was stored in 37°C for 6.5 h, the mixture was filtered through 0.45 um membrane filter and the filtrate was purified by HPLC. The collected fraction was lyophilized to result the product 40 as trifluoroacetic acid salt (28.8

20 mg, 90%): <sup>1</sup>H NMR (D<sub>2</sub>O) δ 7.96 (d, 2H, *J* = 8.7 Hz), 7.32 (d, 2H, *J* = 8.7 Hz), 5.89 (d, 1H, *J* = 5.1 Hz), 5.66 (br, 1H), 5.27 (m, 1H), 4.97 (m, 1H), 4.23-4.12 (m, 2H), 4.08 (s, 3H), 4.06-3.10 (m, 14H), 3.03 (dd, 1H; *J* = 14.1 and 6.6 Hz), 2.78-1.97 (m, 9H), 1.66 (d, 3H, *J* = 6.9 Hz), 1.03 (d, 3H, *J* = 7.5 Hz), 1.01 (d, 3H, *J* = 6.9 Hz); <sup>31</sup>P NMR (CD<sub>3</sub>CN+TFA) δ 20.0, 19.8; MS (ESI) 748 (M+H).

Scheme 8







48A: a minor diastereomer (GS277932)

48B: a major diastereomer (GS277933)

### Example 32

Compound 42: The dibenzyl phosphonate **41** (947 mg, 1.21 mmol) was treated with DABCO (140.9 mg, 1.26 mmol, Aldrich) in 4.5 mL toluene to obtain the monoacid (890 mg, 106%).

The crude monoacid (890 mg) was dried by evaporation with toluene twice and dissolved in DMF (5.3 mL) with ethyl (*S*)-lactate (0.3 mL, 2.65 mmol, Aldrich) and pyBOP (945 mg, 1.82 mmol, Aldrich) at room temperature. After diisopropylethylamine (0.85 mL, 4.88 mmol, Aldrich) was added, the solution was stirred at room temperature for 4 h and concentrated

under reduced pressure to a half volume. The resulting solution was diluted with 5% aqueous HCl (30 mL) and the product was extracted with EtOAc (30 mL x 3). After the combined extracts were dried (MgSO<sub>4</sub>) and concentrated, the residue was chromatographed on silica gel to afford the compound **42** (686 mg, 72%) as a mixture of two diastereomers (2:3 ratio): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.46-7.32 (m, 5H), 7.13 (d, 2H, *J* = 8.1 Hz), 6.85 (t, 2H, *J* = 8.1 Hz), 5.65 (m, 1H), 5.35-4.98 (m, 4H), 4.39 (d, 0.8H, *J* = 10.2 Hz), 4.30-4.14 (m, 3.2H), 3.98 (dd, 1H, *J* = 9.3 and 6.0 Hz), 3.92-3.78 (m, 3H), 3.78-3.55 (m, 3H), 3.16-2.68 (m, 6H), 1.85 (m, 1H), 1.74-1.55 (m, 2H), 1.56 (d, 1.8H, *J* = 7.2 Hz), 1.49 (d, 1.2H), 1.48 (s, 9H), 1.30-1.23 (m, 3H), 0.88 (d, 3H, *J* = 6.3 Hz), 0.87 (d, 3H, *J* = 6.3 Hz); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 20.8 (0.4P), 19.5 (0.6P); MS (ESI) 793 (M+H).

Example 33

Compound 45: A solution of compound 42 (101 mg, 0.127 mmol) and trifluoroacetic acid (0.27 mL, 3.5 mmol, Aldrich) in  $\text{CH}_2\text{Cl}_2$  (0.6 mL) was stirred at 0°C for 3.5 h and concentrated under reduced pressure. The resulting residue was dried in vacuum to result the crude amine as TFA salt.

A solution of the crude amine salt and triethylamine (0.072 mL, 0.52 mmol, Aldrich) in  $\text{CH}_2\text{Cl}_2$  (1 mL) was stirred at 0°C as the sulfonyl chloride 42 (37 mg, 0.14 mmol) was added. After the solution was stirred at 0°C for 4 h and 0.5 h at room temperature, the reaction mixture was diluted with saturated  $\text{NaHCO}_3$  (20 mL) and extracted with EtOAc (20 mL x 1; 15 mL x 2). The combined organic fractions were washed with saturated NaCl solution, dried ( $\text{MgSO}_4$ ), and concentrated under reduced pressure. Purification by chromatography on silica gel provided the sulfonamide 45 (85 mg, 72%) as a mixture of two diastereomers (~1:2 ratio):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.45-7.31 (m, 7H), 7.19 (d, 1H,  $J$  = 8.4 Hz), 7.12 (d, 2H,  $J$  = 7.8 Hz), 6.85 (m, 2H), 5.65 (d, 1H,  $J$  = 5.4 Hz), 5.34-5.16 (m, 2H), 5.13-4.97 (m, 2H), 4.97-4.86 (m, 1H), 4.38 (d, 0.7H,  $J$  = 10.8 Hz), 4.29-4.12 (m, 3.3H), 3.96 (dd, 1H,  $J$  = 9.3 and 6.3 Hz), 3.89 (s, 3H), 3.92-3.76 (m, 3H), 3.76-3.64 (m, 2H), 3.64-3.56 (br, 1H), 3.34-3.13 (m, 1H), 3.11-2.70 (m, 6H), 2.34 (s, 3H), 1.86 (m, 1H,  $J$  = 7.0 Hz), 1.75-1.58 (m, 2H), 1.56 (d, 2H,  $J$  = 7.2 Hz), 1.49 (d, 1H,  $J$  = 7.2 Hz), 1.29-1.22 (m, 3H), 0.94 (d, 3H,  $J$  = 6.6 Hz), 0.90 (d, 3H,  $J$  = 6.9 Hz);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.7 (0.3P), 19.5 (0.7P); MS (ESI) 921 (M+H).

Example 34

Compound 46: Compound 45 (257 mg, 0.279 mmol) was stirred in a saturated solution of ammonia in ethanol (5 mL) at 0°C for 15 min and the solution was concentrated under reduced pressure. Purification of the residue by chromatography on silica gel provided compound 46 (2.6 mg, 84%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.48-7.34 (m, 4H), 7.22-7.05 (m, 5H), 7.01 (d, 1H,  $J$  = 8.1 Hz), 6.87-6.80 (m, 2H), 5.68 (d, 1H,  $J$  = 4.8 Hz), 5.32 (dd, 1.3H,  $J$  = 8.7 and 1.8 Hz), 5.22 (d, 0.7H,  $J$  = 9.0 Hz), 5.11-5.00 (m, 3H), 4.47-4.14 (m, 4H), 4.00 (dd, 1H,  $J$  = 9.9 and 6.6 Hz), 3.93 (s, 3H), 3.95-3.63 (m, 5H), 3.07-2.90 (m, 4H), 2.85-2.75 (m, 1H), 2.75-2.63 (m, 2H), 1.88-1.67 (m, 3H), 1.65-1.55 (m, 2H), 1.57 (d, 2H,  $J$  = 6.9 Hz), 1.50 (d, 1H,  $J$  = 7.2 Hz), 1.31-1.20 (m, 3H), 0.95 (d, 3H,  $J$  = 6.6 Hz), 0.88 (d, 3H,  $J$  = 6.3 Hz);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  20.7 (0.3P), 19.6 (0.7P); MS (ESI) 879 (M+H).

Example 35

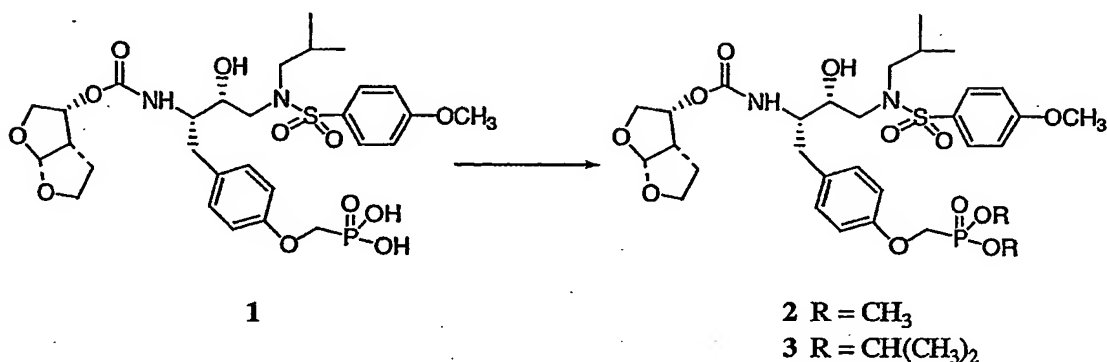
Compound 47: A mixture of compound 46 (176 mg, 0.200 mmol) and 10% Pd/C (9.8 mg, Aldrich) in EtOAc (4 mL) and ethanol (1 mL) was stirred under H<sub>2</sub> atmosphere for 3 h at room temperature. After the mixture was filtered through celite, the filtrate was concentrated to dryness to afford compound 47 (158 mg, 100%) as white powder: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.30-7.16 (m, 2H), 7.12 (d, 2H, *J* = 7.5 Hz), 7.01 (d, 1H, *J* = 7.8 Hz), 6.84 (d, 2H, *J* = 7.5 Hz), 5.66 (d, 1H, *J* = 4.5 Hz), 5.13-4.97 (m, 2H), 4.38-4.10 (m, 4H), 3.93 (s, 3H), 4.02-3.66 (m, 6H), 3.13-2.69 (m, 7H), 1.96-1.50 (m, 3H), 1.57 (d, 3H, *J* = 6.6 Hz), 1.26 (t, 3H, *J* = 7.2 Hz), 0.93 (d, 3H, *J* = 6.0 Hz), 0.88 (d, 3H, *J* = 6.0 Hz); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 20.1; MS (ESI) 789 (M+H).

Example 36

Compound 48A and 48B: A solution of pyBOP (191 mg, 0.368 mmol, Aldrich) and diisopropylethylamine (0.1 mL, 0.574 mmol, Aldrich) in DMF (35 mL) was stirred at room temperature as a solution of compound 47 (29 mg, 0.036 mmol) in DMF (5.5 mL) was added over 16 h. After addition, the solution was stirred at room temperature for 3 h and concentrated under reduced pressure. The residue was dissolved in ice-cold water and extracted with EtOAc (20 mL x 1; 10 mL x 2). The combined extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel followed by preparative TLC gave two isomers of structure 48 (1.0 mg, 3.6% and 3.6 mg, 13%). Isomer 48A: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.39 (m, 1H), 7.12 (br, 1H), 7.01 (d, 2H, *J* = 8.1 Hz), 6.98 (br, 1H), 6.60 (d, 2H, *J* = 8.1 Hz), 5.75 (d, 1H, *J* = 5.1 Hz), 5.37-5.28 (m, 2H), 5.18 (q, 1H, *J* = 8.7 Hz), 4.71 (dd, 1H, *J* = 14.1 and 7.5 Hz), 4.29 (m, 3H), 4.15-4.06 (m, 1H), 3.99 (s, 3H), 4.05-3.6 (m, 5H), 3.35 (m, 1H), 3.09 (br, 1H), 2.90-2.78 (m, 3H), 2.2-2.0 (m, 3H), 1.71 (d, 3H, *J* = 6.6 Hz), 1.34 (t, 3H, *J* = 6.9 Hz), 1.01 (d, 3H, *J* = 6.3 Hz), 0.95 (d, 3H, *J* = 6.3 Hz); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 17.8; MS (ESI) 793 (M+Na); isomer 48B: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.46 (d, 1H, *J* = 9.3 Hz), 7.24 (br, 1H), 7.00 (d, 2H, *J* = 8.7 Hz), 6.91 (d, 1H, *J* = 8.7 Hz), 6.53 (d, 2H, *J* = 8.7 Hz), 5.74 (d, 1H, *J* = 5.1 Hz), 5.44 (m, 1H), 5.35 (d, 1H, *J* = 9.0 Hz), 5.18 (q, 1H, *J* = 7.2 Hz), 4.68 (dd, 1H, *J* = 14.4 and 6.3 Hz), 4.23 (m, 3H), 4.10 (m, 1H), 4.04 (s, 3H), 3.77-4.04 (m, 6H), 3.46 (dd, 1H, *J* = 12.9 and 11.4 Hz), 3.08 (br, 1H), 2.85 (m, 2H), 2.76 (dd, 1H, *J* = 12.9 and 4.8 Hz), 1.79-2.11 (m, 3H), 1.75 (d, 3H, *J* = 6.6 Hz), 1.70 (m, 2H),

1.27 (t, 3H,  $J = 6.9$  Hz), 1.01 (d, 3H,  $J = 6.6$  Hz), 0.93 (d, 3H,  $J = 6.6$  Hz);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  15.4; MS (ESI) 793 ( $\text{M}+\text{Na}$ ).

### Example 1



### Example 1A

Dimethylphosphonic ester 2 ( $\text{R} = \text{CH}_3$ ): To a flask was charged with phosphonic acid 1 (67 mg, 0.1 mmol), methanol (0.1 mL, 2.5 mmol) and 1, 3-dicyclohexylcarbodiimide (83 mg, 0.4 mmol), then pyridine (1 mL) was added under  $\text{N}_2$ . The resulted mixture was stirred at  $-70^\circ\text{C}$  for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was diluted with ethyl acetate and the combined organic phase was washed with  $\text{NH}_4\text{Cl}$ , brine and water, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified by chromatography on silica gel (isopropanol/ $\text{CH}_2\text{Cl}_2$ , 1% to 7%) to give 2 (39 mg, 56 %) as a white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71(d,  $J = 8.7$  Hz, 2H), 7.15 (d,  $J = 8.7\text{Hz}$ , 2H), 7.00 (d,  $J = 8.7$  Hz, 2H), 6.87 (d,  $J = 8.7$  Hz, 2H), 5.65 (d,  $J = 5.1$  Hz, 1H), 5.10-4.92 (m, 4H), 4.26 (d,  $J = 9.9$  Hz, 2H), 3.96 -3.65 (m overlapping s, 15H), 3.14-2.76 (m, 7H), 1.81-1.55 (m, 3H), 0.91 (d,  $J = 6.6$  Hz, 3H), 0.88 (d,  $J = 6.6$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  21.7; MS (ESI) 723 ( $\text{M}+\text{Na}$ ).

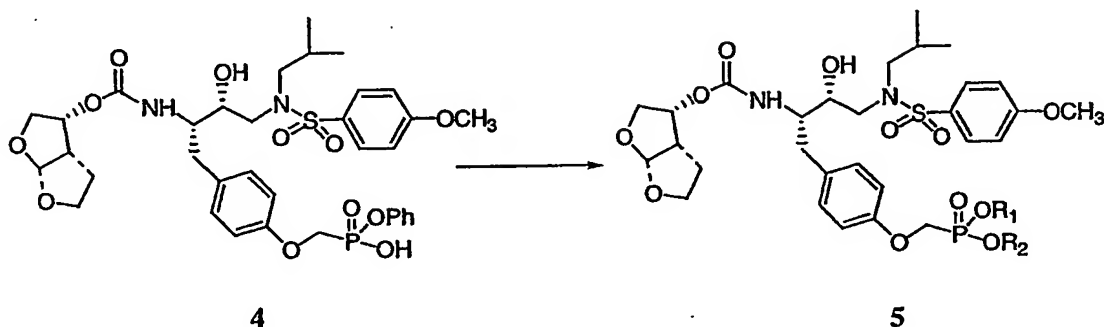
### Example 1B

Diisopropylphosphonic ester 3 ( $\text{R} = \text{CH}(\text{CH}_3)_2$ ) was synthesized in the same manner in 60% yield.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71(d,  $J = 8.7$  Hz, 2H), 7.15 (d,  $J = 8.7\text{Hz}$ , 2H), 7.15 (d,  $J = 8.7$  Hz, 2H), 6.99 (d,  $J = 8.7$  Hz, 2H), 6.87 (d,  $J = 8.7$  Hz, 2H), 5.66 (d,  $J = 5.1$  Hz, 1H), 5.08-4.92 (m, 3H), 4.16 (d,  $J = 10.5$  Hz, 2H), 3.98 -3.68 (m overlapping s, 9H), 3.16-2.78 (m, 7H),

1.82-1.56 (m, 3H), 1.37 (t,  $J = 6.3$  Hz, 6H), 0.93 (d,  $J = 6.6$  Hz, 3H), 0.88 (d,  $J = 6.6$  Hz, 3H);  
 $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.3; MS (ESI) 779 ( $\text{M}+\text{Na}$ ).

### Example 2

5



Compound	R <sub>1</sub>	R <sub>2</sub>
5a	OPh	mix-Hba-Et
5b	OPh	( <i>S</i> )-Hba-Et
5c	OPh	( <i>S</i> )-Hba-tBu
5d	OPh	( <i>S</i> )-Hba-EtMor
5e	OPh	( <i>R</i> )-Hba-Et

### Example 2A

10 Monolactate 5a ( $\text{R}_1 = \text{OPh}$ ,  $\text{R}_2 = \text{Hba-Et}$ ): To a flask was charged with monophenyl phosphonate 4 (250 mg, 0.33 mmol), 2-hydroxy-*n*-butyric acid ethyl ester (145 mg, 1.1 mmol) and 1, 3-dicyclohexylcarbodiimide (226 mg, 1.1 mmol), then pyridine (2.5 mL) was added under  $\text{N}_2$ . The resulted mixture was stirred at 60–70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was

15 evaporated. The residue was diluted with ethyl acetate and the combined organic phase was washed with  $\text{NH}_4\text{Cl}$ , brine and water, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified by chromatography on silica gel ( $\text{EtOAc}/\text{CH}_2\text{Cl}_2$ , 1:1) to give 5a (150 mg, 52 %) as a white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.70 (d,  $J = 8.7$  Hz, 2H), 7.37-7.19 (m, 5H), 7.14 (d,  $J = 8.7$  Hz, 2H), 7.00 (d,  $J = 8.7$  Hz, 2H), 6.91 (d,  $J = 8.7$  Hz, 1H), 6.86 (d,  $J = 8.7$

20 Hz, 1H), 5.65 (m, 1H), 5.10-4.95 (m, 3H), 4.57-4.39 (m, 2H), 4.26 (m, 2H), 3.96-3.68 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.55 (m, 5H), 1.21 (m, 3H), 1.04-0.86 (m, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.5 and 15.1; MS (ESI) 885 ( $\text{M}+\text{Na}$ ).

Example 2B

Monolactate **5b** (R1 = OPh, R2 = (*S*)-Hba-Et): To a flask was charged with monophenyl phosphonate **4** (600 mg, 0.8 mmol), (*S*)-2-hydroxy-n-butyric acid ethyl ester (317 mg, 2.4 mmol) and 1, 3-dicyclohexylcarbodiimide (495 mg, 2.4 mmol), then pyridine (6 mL) was added under N<sub>2</sub>. The resulted mixture was stirred at 60–70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was diluted with ethyl acetate and the combined organic phase was washed with NH<sub>4</sub>Cl, brine and water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOAc/CH<sub>2</sub>Cl<sub>2</sub>, 1:1) to give **5b** (360 mg, 52 %) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.71 (d, J = 8.7 Hz, 2H), 7.37-7.19 (m, 5H), 7.15 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 5.65 (m, 1H), 5.10-4.95 (m, 3H), 4.57-4.39 (m, 2H), 4.26 (m, 2H), 3.96-3.68 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.55 (m, 5H), 1.23 (m, 3H), 1.04-0.86 (m, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 17.5 and 15.2; MS (ESI) 885 (M+Na).

Example 2C

Monolactate **5c**(R1 = OPh, R2 = (*S*)-Hba-tBu): To a flask was charged with monophenyl phosphonate **4** (120 mg, 0.16 mmol), tert-butyl (*S*)-2-hydroxybutyrate (77 mg, 0.48 mmol) and 1, 3-dicyclohexylcarbodiimide (99 mg, 0.48 mmol), then pyridine (1 mL) was added under N<sub>2</sub>. The resulted mixture was stirred at 60–70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was diluted with ethyl acetate and the combined organic phase was washed with NH<sub>4</sub>Cl, brine and water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOAc/CH<sub>2</sub>Cl<sub>2</sub>, 1:1) to give **5c** (68 mg, 48 %) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.71 (d, J = 8.7 Hz, 2H), 7.37-7.19 (m, 5H), 7.14 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.7 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 5.64 (m, 1H), 5.10-4.95 (m, 3H), 4.57-4.39 (m, 2H), 4.26 (m, 2H), 3.96-3.68 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.55 (m, 5H), 1.44 (d, J = 11 Hz, 9H), 1.04-0.86 (m, 9H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 17.5 and 15.2; MS (ESI) 913 (M+Na).

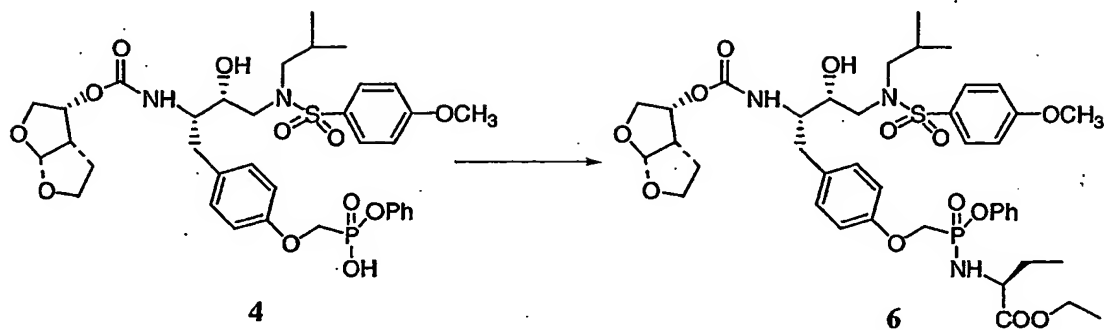
Example 2D

Monolactate **5d** (R1 = OPh, R2 = (*S*)-Lac-EtMor): To a flask was charged with monophenyl phosphonate **4** (188 mg, 0.25 mmol), (*S*)-lactate ethylmorpholine ester (152 mg, 0.75 mmol)

and 1, 3-dicyclohexylcarbodiimide (155 mg, 0.75 mmol), then pyridine (2mL) was added under N<sub>2</sub>. The resulted mixture was stirred at 60–70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was washed with ethyl acetate and the combined organic phase was washed with NH<sub>4</sub>Cl, brine and water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by chromatography on silica gel (isopropanol/CH<sub>2</sub>Cl<sub>2</sub>, 1:9) to give **5d** (98 mg, 42 %) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.72 (d, J = 8.7 Hz, 2H), 7.34-7.20 (m, 5H), 7.15 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 1H), 6.87 (d, J = 8.7 Hz, 1H), 5.65 (m, 1H), 5.21-4.99 (m, 3H), 4.57-4.20 (m, 4H), 3.97 -3.63 (m overlapping s, 13H), 3.01-2.44 (m, 13H), 1.85-1.50 (m, 6H), 0.92 (d, J = 6.5 Hz, 3H), 0.88 (d, J = 6.5, 3H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 17.4 and 15.3; MS (ESI) 934(M).

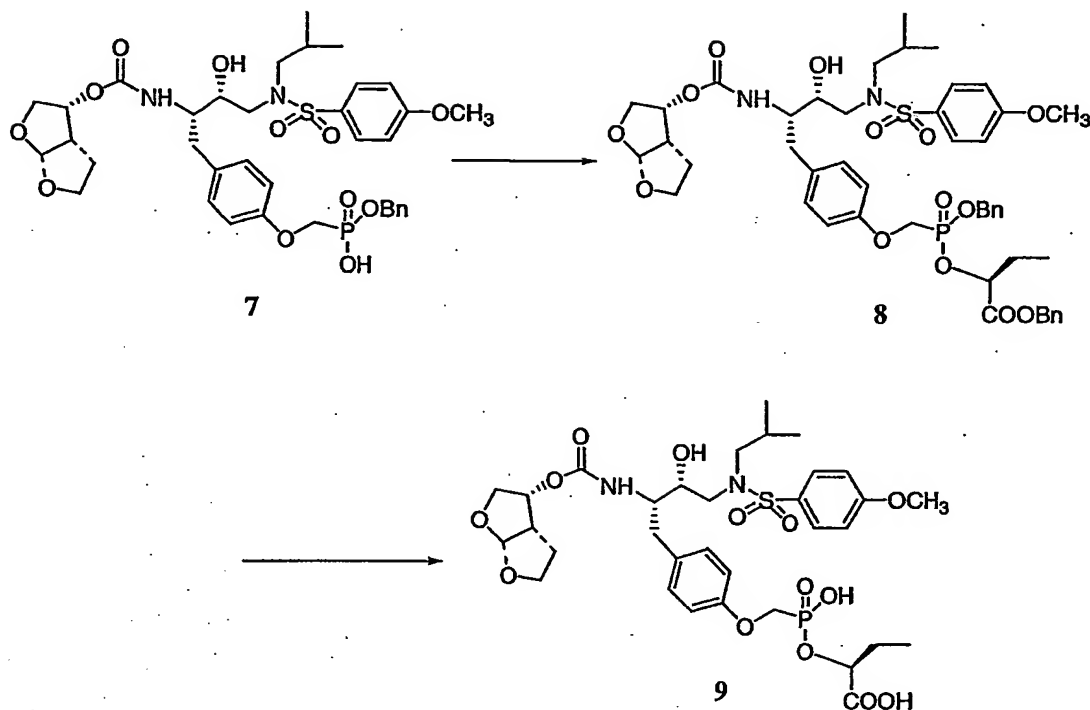
#### Example 2E

Monolactate **5e** (R1 = OPh, R2 = (*R*)-Hba-Et): To a flask was charged with monophenyl phosphonate **4** (600 mg, 0.8 mmol), (*R*)-2-hydroxy-n-butyric acid ethyl ester (317 mg, 2.4 mmol) and 1, 3-dicyclohexylcarbodiimide (495 mg, 2.4 mmol), then pyridine (6 mL) was added under N<sub>2</sub>. The resulted mixture was stirred at 60–70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was diluted with ethyl acetate and the combined organic phase was washed with NH<sub>4</sub>Cl, brine and water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOAc/CH<sub>2</sub>Cl<sub>2</sub>, 1:1) to give **5e** (345 mg, 50 %) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.70 (d, J = 8.7 Hz, 2H), 7.37-7.19 (m, 5H), 7.15 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 5.65 (m, 1H), 5.10-4.95 (m, 3H), 4.57-4.39 (m, 2H), 4.26 (m, 2H), 3.96 -3.68 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.55 (m, 5H), 1.23 (m, 3H), 1.04-0.86 (m, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 17.5 and 15.1; MS (ESI) 885 (M+Na).

**Example 3**

Monoamidate 6: To a flask was charged with monophenyl phosphonate 4 (120 mg, 0.16 mmol), L-alanine butyric acid ethyl ester hydrochloride (160 mg, 0.94 mmol) and 1, 3-dicyclohexylcarbodiimide (132 mg, 0.64 mmol), then pyridine (1 mL) was added under N<sub>2</sub>. The resulted mixture was stirred at 60–70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was diluted with ethyl acetate and the combined organic phase was washed with NH<sub>4</sub>Cl, brine and water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by chromatography on silica gel (isopropanol/CH<sub>2</sub>Cl<sub>2</sub>, 1:9) to give 6 (55 mg, 40 %) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.72 (d, J = 8.7 Hz, 2H), 7.37–7.23 (m, 5H), 7.16 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.90–6.83 (m, 2H), 5.65 (d, J = 5.1 Hz, 1H), 5.10–4.92 (m, 3H), 4.28 (m, 2H), 3.96–3.68 (m overlapping s, 9H), 3.15–2.77 (m, 7H), 1.81–1.55 (m, 5H), 1.23 (m, 3H), 1.04–0.86 (m, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 20.7 and 19.6; MS (ESI) 884(M+Na).



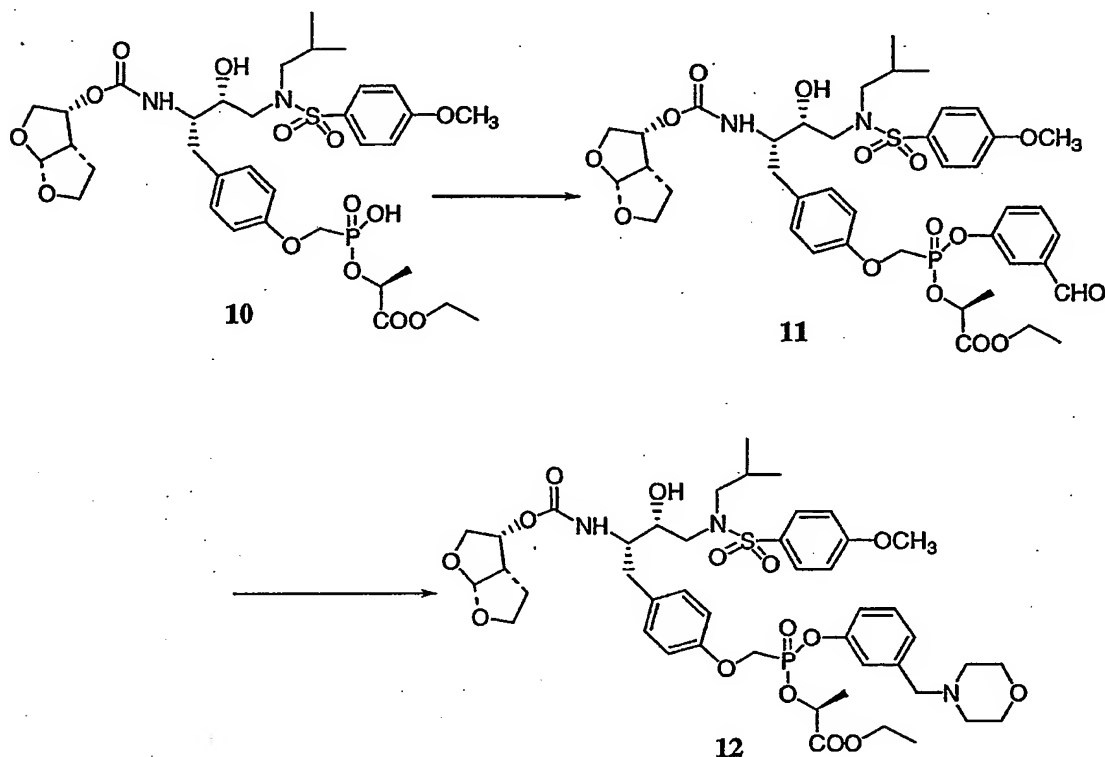
**Example 4A**

Compound 8: To a stirred solution of monobenzyloxy phosphonate 7 (195 mg, 0.26mmol) in 1 mL of DMF at room temperature under N<sub>2</sub> was added benzyl-(s)-lactate (76 mg, 0.39 mmol) and PyBOP (203 mg, 0.39mmol), followed by DIEA (181μL, 1 mmol). After 3 h, the solvent was removed under reduced pressure, and the resulting crude mixture was purified by chromatography on silica gel (ethyl acetate/hexane 1:1) to give 8 (120 mg, 50%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.71 (d, J = 8.7 Hz, 2H), 7.38-7.34 (m, 5H), 7.12 (d, J = 8.7 Hz, 2H), 6.99 (d, J = 8.7 Hz, 2H), 6.81(d, J = 8.7 Hz, 2H), 5.64 (d, J = 5.4 Hz, 1H), 5.24-4.92 (m, 7H), 4.28 (m, 2H), 3.96 -3.67 (m overlapping s, 9H), 3.16-2.76 (m, 7H), 1.95-1.62 (m, 5H), 0.99-0.87 (m, 9H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 21.0 and 19.7; MS (ESI) 962 (M+Na).

**Example 4B**

Compound 9: A solution of compound 8 (100 mg) was dissolved in EtOH/ EtOAc (9 mL/ 3mL), treated with 10 % Pd/C (10 mg) and was stirred under H<sub>2</sub> atmosphere (balloon) for 1.5 h. The catalyst was removed by filtration through celite. The filtered was evaporated under reduced pressure, the residue was triturated with ether and the solid was collected by filtration to afford the compound 9 (76mg, 94%) as a white solid. <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.76 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 5.59 (d, J = 5.4 Hz, 1H), 5.03-4.95 (m, 2H), 4.28 (m, 2H), 3.90 -3.65 (m overlapping s, 9H).

9H), 3.41 (m, 2H), 3.18-2.78 (m, 5H), 2.44 (m, 1H), 1.96 (m, 3H), 1.61 (m, 2H), 1.18 (m, 3H), 0.93 (d,  $J = 6.3$  Hz, 3H), 0.87 (d,  $J = 6.3$  Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  18.3; MS (ESI) 782 ( $\text{M}+\text{Na}$ ).



#### Example 5A

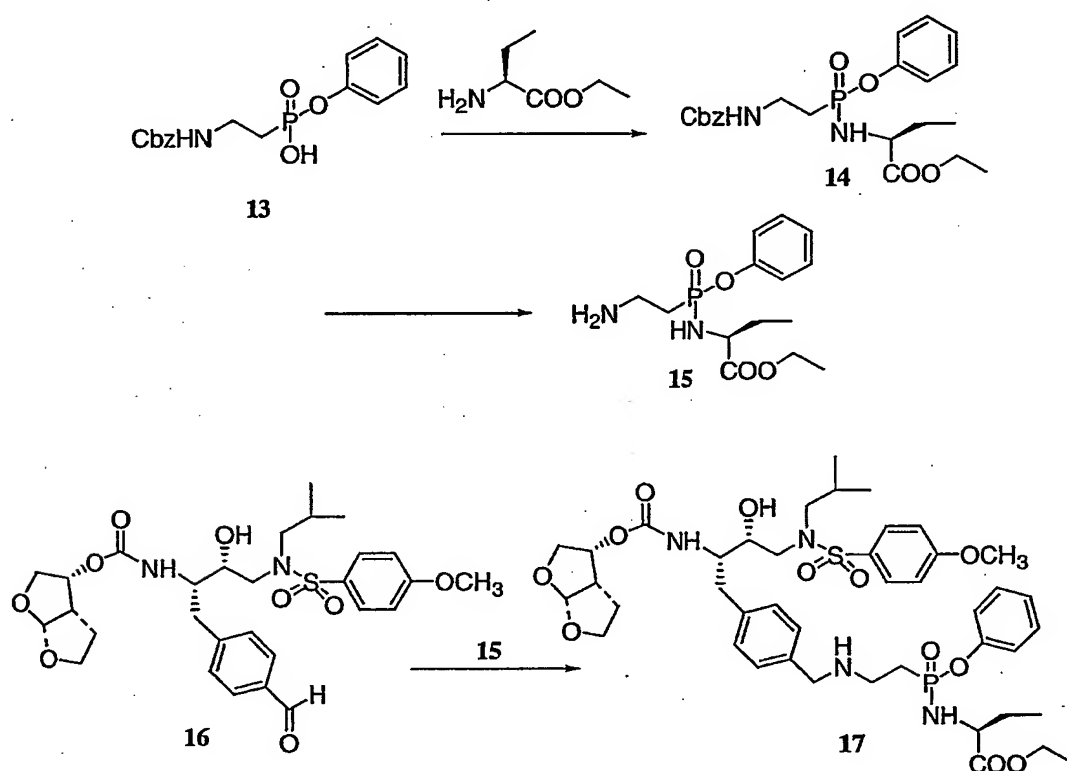
Compound 11: To a stirred solution of compound 10 (1 g, 1.3mmol) in 6 mL of DMF at room temperature under  $\text{N}_2$  was added 3-hydroxybenzaldehyde (292 mg, 2.6 mmol) and PyBOP (1 g, 1.95mmol), followed by DIEA (0.9 mL, 5.2 mmol). After 5 h, the solvent was removed under reduced pressure, and the resulting crude mixture was purified by chromatography on silica gel (ethyl acetate/hexane 1:1) to give 11 (800 mg, 70%) as a white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  9.98 (s, 1H), 7.79-6.88 (m, 12H), 5.65 (m, 1H), 5.21-4.99 (m, 3H), 4.62-4.16 (m, 4H), 3.99-3.61 (m overlapping s, 9H), 3.11-2.79 (m, 5H), 1.85-1.53 (m, 6H), 1.25 (m, 3H), 0.90 (m, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.9 and 15.9; MS (ESI) 899 ( $\text{M}+\text{Na}$ ).

#### Example 5B

Compound 12: To a stirred solution of compound 11 (920 mg, 1.05 mmol) in 10 mL of ethyl acetate at room temperature under  $\text{N}_2$  was added morpholine (460 mg, 5.25 mmol) and acetic

acid (0.25 mL, 4.2 mmol), followed by sodium cyanoborohydride (132 mg, 2.1 mmol). After 20h, the solvent was removed under reduced pressure, and the residue was diluted with ethyl acetate and the combined organic phase was washed with  $\text{NH}_4\text{Cl}$ , brine and water, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified by chromatography on silica gel (isopropanol /  $\text{CH}_2\text{Cl}_2$ , 6%) to give 12 (600 mg, 60%) as a white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71 (d,  $J = 8.7$  Hz, 2H), 7.27 (m, 4H), 7.15 (d,  $J = 8.7$  Hz, 2H), 6.95 (d,  $J = 8.7$  Hz, 2H), 6.89 (m, 2H), 5.65 (m, 1H), 5.21-5.02 (m, 3H), 4.58-4.38 (m, 2H), 4.21-4.16 (m, 2H), 3.99-3.63 (m overlapping s, 15H), 3.47 (s, 2H), 3.18-2.77 (m, 7H), 2.41 (s, 4H), 1.85-1.53 (m, 6H), 1.25 (m, 3H), 0.90 (m, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.4 and 15.2; MS (ESI) 971 ( $\text{M}+\text{Na}$ ).

10



#### Example 6A

Compound 14: To a stirred solution of compound 13 (1 g, 3 mmol) in 30 mL of acetonitrile at room temperature under  $\text{N}_2$  was added thionyl chloride (0.67 mL, 9 mmol). The resulted mixture was stirred at 60-70°C for 0.5 h. After cooled to room temperature, the solvent was removed under reduced pressure, and the residue was added 30 mL of DCM, followed by DIEA (1.7 mL, 10 mmol), L-alanine butyric acid ethyl ester hydrochloride (1.7 g, 10 mmol) and TEA (1.7 mL, 12 mmol). After 4h at room temperature, the solvent was removed under

reduced pressure, and the residue was diluted with DCM and washed with brine and water, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified by chromatography on silica gel (Hexane/EtOAc 1:1) to give 14 (670 mg, 50%) as a yellow oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.33-7.11 (m, 10H), 5.70 (m, 1H), 5.10 (s, 2H), 4.13-3.53 (m, 5H), 2.20-2.10 (m, 2H), 1.76-1.55 (m, 2H), 1.25-1.19 (m, 3H), 0.85-0.71 (m, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  30.2 and 29.9; MS (ESI) 471 (M+Na).

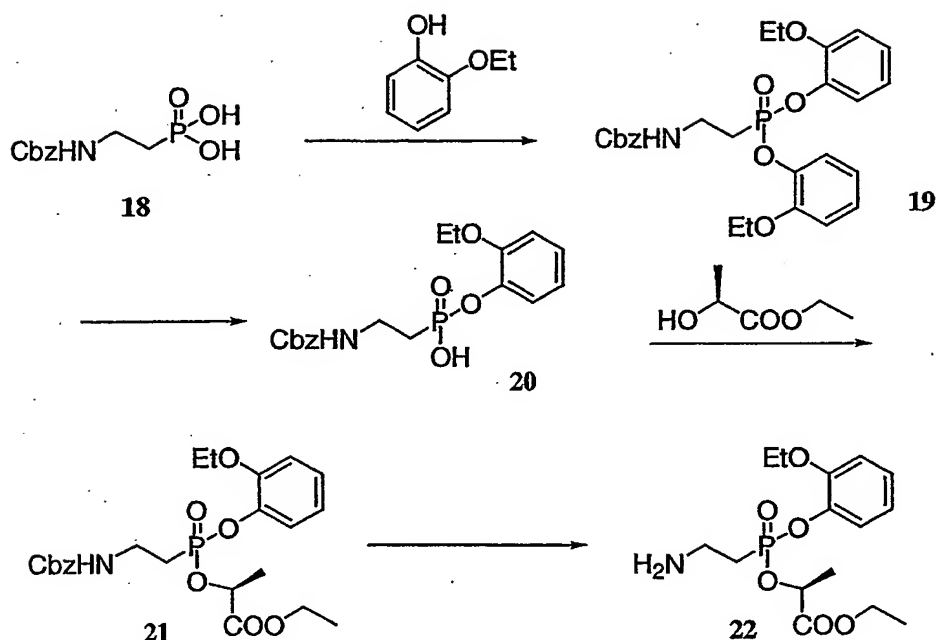
#### Example 6B

Compound 15: A solution of compound 14 (450mg) was dissolved in 9 mL of EtOH, then 0.15 mL of acetic acid and 10 % Pd/C (90 mg) was added. The resulted mixture was stirred under  $\text{H}_2$  atmosphere (balloon) for 4 h. After filtration through celite, the filtered was evaporated under reduced pressure to afford the compound 15 (300mg, 95%) as a colorless oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.29-7.12 (m, 5H), 4.13-3.53 (m, 5H), 2.20-2.10 (m, 2H), 1.70-1.55 (m, 2H), 1.24-1.19 (m, 3H), 0.84-0.73(m, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  29.1 and 28.5; MS (ESI) 315 (M+1).

#### Example 6C

Monoamidate 17: To a stirred solution of compound 16 (532 mg, 0.9 mmol) in 4 mL of 1,2-dichloroethane was added compound 15 (300 mg, 0.96 mmol) and  $\text{MgSO}_4$  (50 mg), the resulted mixture was stirred at room temperature under argon for 3h, then acetic acid (1.3 mL, 23 mmol) and sodium cyanoborohydride (1.13 g, 18 mmol) were added. The reaction mixture was stirred at room temperature for 1 h under argon. Then aqueous  $\text{NaHCO}_3$  (50 mL) was added, and the mixture was extracted with ethyl acetate, and the combined organic layers were washed with brine and water, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified by chromatography on silica gel (EtOH / EtOAc, 1/9) to give 17 (600 mg, 60%) as a white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.73 (d, J = 8.7 Hz, 2H), 7.33-7.13 (m, 9H), 7.00 (d, J = 8.7 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.11-4.98 (m, 2H), 4.22 -3.68 (m, overlapping s, 15H), 3.20-2.75 (m, 9H), 2.21-2.10 (m, 2H), 1.88-1.55(m, 5H), 1.29-1.19 (m, 3H), 0.94-0.70 (m, 9H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  31.8 and 31.0; MS (ESI) 889 (M).

#### Example 7

**Example 7A**

Compound 19: To a stirred solution of compound 18 (3.7 g, 14.3 mmol) in 70 mL of acetonitrile at room temperature under N<sub>2</sub> was added thionyl chloride (6.3 mL, 86 mmol). The resulted mixture was stirred at 60-70°C for 2 h. After cooled to room temperature, the solvent was removed under reduced pressure, and the residue was added 150 mL of DCM, followed by TEA (12 mL, 86 mmol) and 2-ethoxyphenol (7.2 mL, 57.2 mmol). After 20h at room temperature, the solvent was removed under reduced pressure, and the residue was diluted with ethyl acetate and washed with brine and water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by chromatography on silica gel (DCM/EtOAc 9:1) to give 19 (4.2 g, 60%) as a yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.32-6.83 (m, 13H), 5.22 (m, 1H), 5.12 (s, 2H), 4.12-3.73 (m, 6H), 2.52-2.42 (m, 2H), 1.41-1.37 (m, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 25.4; MS (ESI) 522 (M+Na).

**Example 7B**

Compound 20: A solution of compound 19 (3 g, 6 mmol) was dissolved in 70 mL of acetonitrile at 0°C, then 2N NaOH (12 mL, 24 mmol) was added dropwisely. The reaction mixture was stirred at room temperature for 1.5 h. Then the solvent was removed under reduced pressure, and the residue diluted with water and extracted with ethyl acetate. The aqueous layer was acidified with conc. HCl to PH = 1, then extracted with ethyl acetate,

combined the organic layer and dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give compound **20** (2 g, 88%) as a off-white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.33-6.79 (m, 9H), 5.10 (s, 2H), 4.12-3.51 (m, 6H), 2.15-2.05 (m, 2H), 1.47-1.33 (m, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  30.5; MS (ESI) 380 (M+1).

5

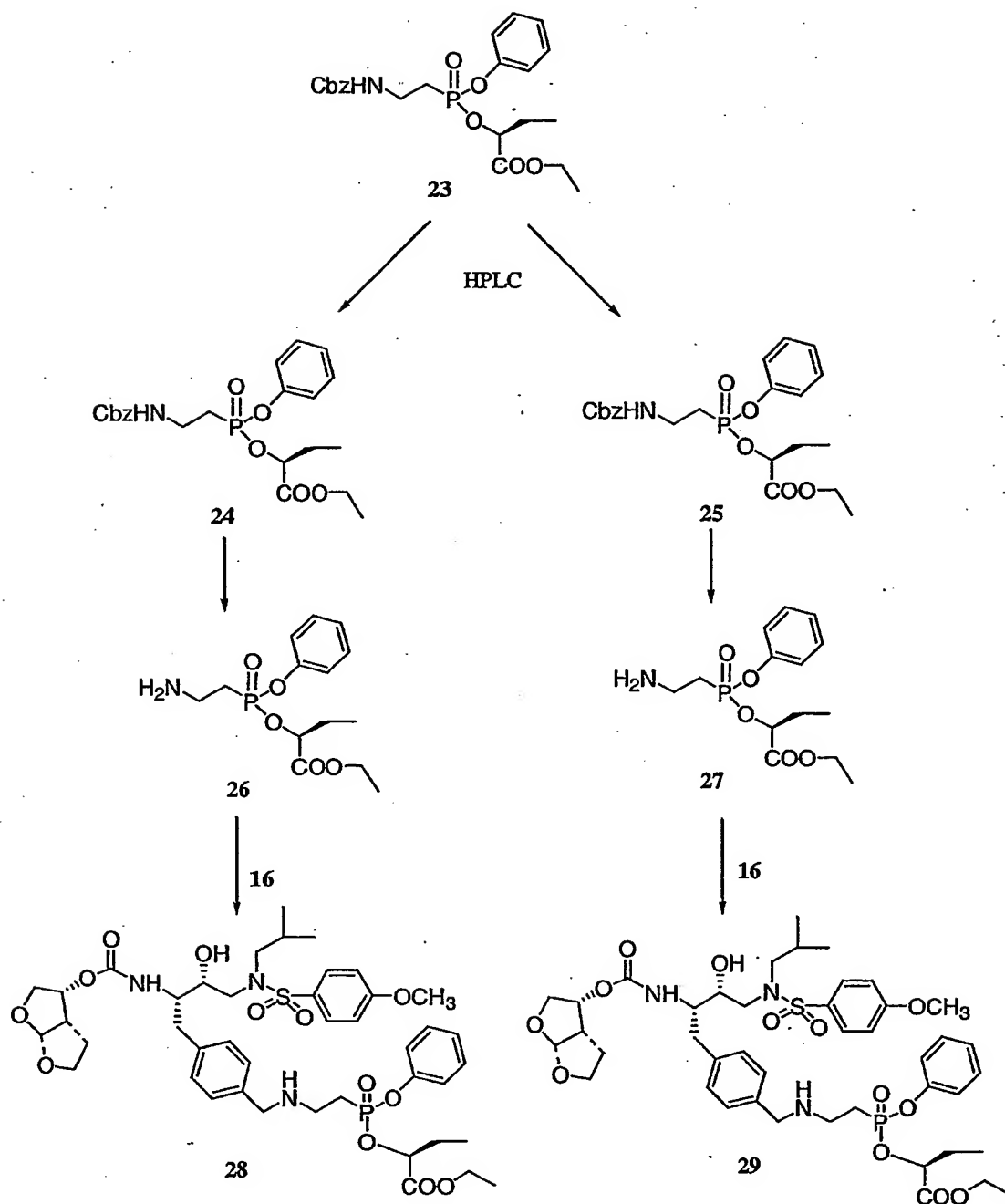
#### Example 7C

Compound **21**: To a stirred solution of compound **20** (1 g, 2.6 mmol) in 20 mL of acetonitrile at room temperature under  $\text{N}_2$  was added thionyl chloride (1.1 mL, 15.6 mmol). The resulted mixture was stirred at 60-70°C for 45 min. After cooled to room temperature, the solvent was removed under reduced pressure, and the residue was added 25 mL of DCM, followed by TEA (1.5 mL, 10.4 mmol) and (S) lactate ethyl ester (0.9 mL, 7.8 mmol). After 20h at room temperature, the solvent was removed under reduced pressure, and the residue was diluted with DCM and washed with brine and water, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The residue was purified by chromatography on silica gel (DCM / EtOAc 3:1) to give **21** (370 mg, 30%) as a yellow oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.33- 6.84 (m, 9H), 6.17-6.01 (m, 1H), 5.70 (m, 1H), 5.18-5.01 (m, 3H), 4.25-4.04 (m, 4H), 3.78-3.57 (m, 2H), 2.38-2.27 (m, 2H), 1.5-1.23 (m, 9H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  29.2 and 27.3; MS (ESI) 502 (M+Na).

#### Example 7D

Compound **22**: A solution of compound **21** (370mg) was dissolved in 8 mL of EtOH, then 0.12 mL of acetic acid and 10 % Pd/C (72 mg) was added. The resulted mixture was stirred under  $\text{H}_2$  atmosphere (balloon) for 4 h. After filtration through celite, the filtered was evaporated under reduced pressure to afford the compound **22** (320mg, 96%) as a colorless oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 7.27- 6.86 (m, 4H), 5.98 (s, 2H), 5.18-5.02 (m, 1H), 4.25-4.06 (m, 4H), 3.34-3.24 (m, 2H), 2.44-2.30 (m, 2H), 1.62-1.24 (m, 9H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  28.3 and 26.8; MS (ESI) 346 (M+1).

25

**Example 8A**

Compound **24**: Compound **23** was purified using a Dynamax SD-200 HPLC system. The mobile phase consisted of acetonitrile: water (65:35, v/v) at a flow rate of 70 mL/ min. The injection volume was 4 mL. The detection was by fluorescence at 245 nm and peak area ratios were used for quantitations. Retention time was 8.2 min for compound **24** as yellow oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.36-7.19 (m, 10H), 5.88 (m, 1H), 5.12 (s, 2H), 4.90-4.86 (m, 1H),

4.26-4.12 (m, 2H), 3.72-3.61(m, 2H), 2.36-2.29 (m, 2H), 1.79-1.74 (m, 2H); 1.27 (t, J = 7.2 Hz, 3H), 0.82 (t, J = 7.2 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  28.3; MS (ESI) 472 (M+Na).

#### Example 8B

- 5 Compound 25 was purified in the same manner and retention time was 7.9 min for compound 25 as yellow oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.34-7.14 (m, 10H), 5.75 (m, 1H), 5.10 (s, 2H), 4.96-4.91 (m, 1H), 4.18-4.12 (m, 2H), 3.66-3.55(m, 2H), 2.29-2.19 (m, 2H), 1.97-1.89 (m, 2H); 1.21 (t, J = 7.2 Hz, 3H), 0.97 (t, J = 7.2 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  26.2; MS (ESI) 472 (M+Na).

10

#### Example 8C

- Compound 26: A solution of compound 24 (1 g) was dissolved in 20 mL of EtOH, then 0.3 mL of acetic acid and 10 % Pd/C (200 mg) was added. The resulted mixture was stirred under  $\text{H}_2$  atmosphere (balloon) for 4 h. After filtration through celite, the filtered was  
15 evaporated under reduced pressure to afford the compound 26 (830mg, 99 %) as a colorless oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.46-7.19 (m, 5H), 4.92-4.81 (m, 1H), 4.24-4.21 (m, 2H), 3.41-3.28 (m, 2H), 2.54-2.38 (m, 2H), 1.79-1.74 (m, 2H), 1.27 (t, J = 7.2 Hz, 3H), 0.80 (t, J = 7.2 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  26.9; MS (ESI) 316 (M+1).

#### 20 Example 8D

- Compound 27: A solution of compound 25 (700g) was dissolved in 14 mL of EtOH, then 0.21 mL of acetic acid and 10 % Pd/C (140 mg) was added. The resulted mixture was stirred under  $\text{H}_2$  atmosphere (balloon) for 4 h. After filtration through celite, the filtered was  
25 evaporated under reduced pressure to afford the compound 27 (510mg, 98 %) as a colorless oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.39-7.18 (m, 5H), 4.98-4.85 (m, 1H), 4.25-4.22 (m, 2H), 3.43-3.28 (m, 2H), 2.59-2.41 (m, 2H), 1.99-1.85 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.02 (t, J = 7.2 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  24.2; MS (ESI) 316 (M+1).

#### Example 8E

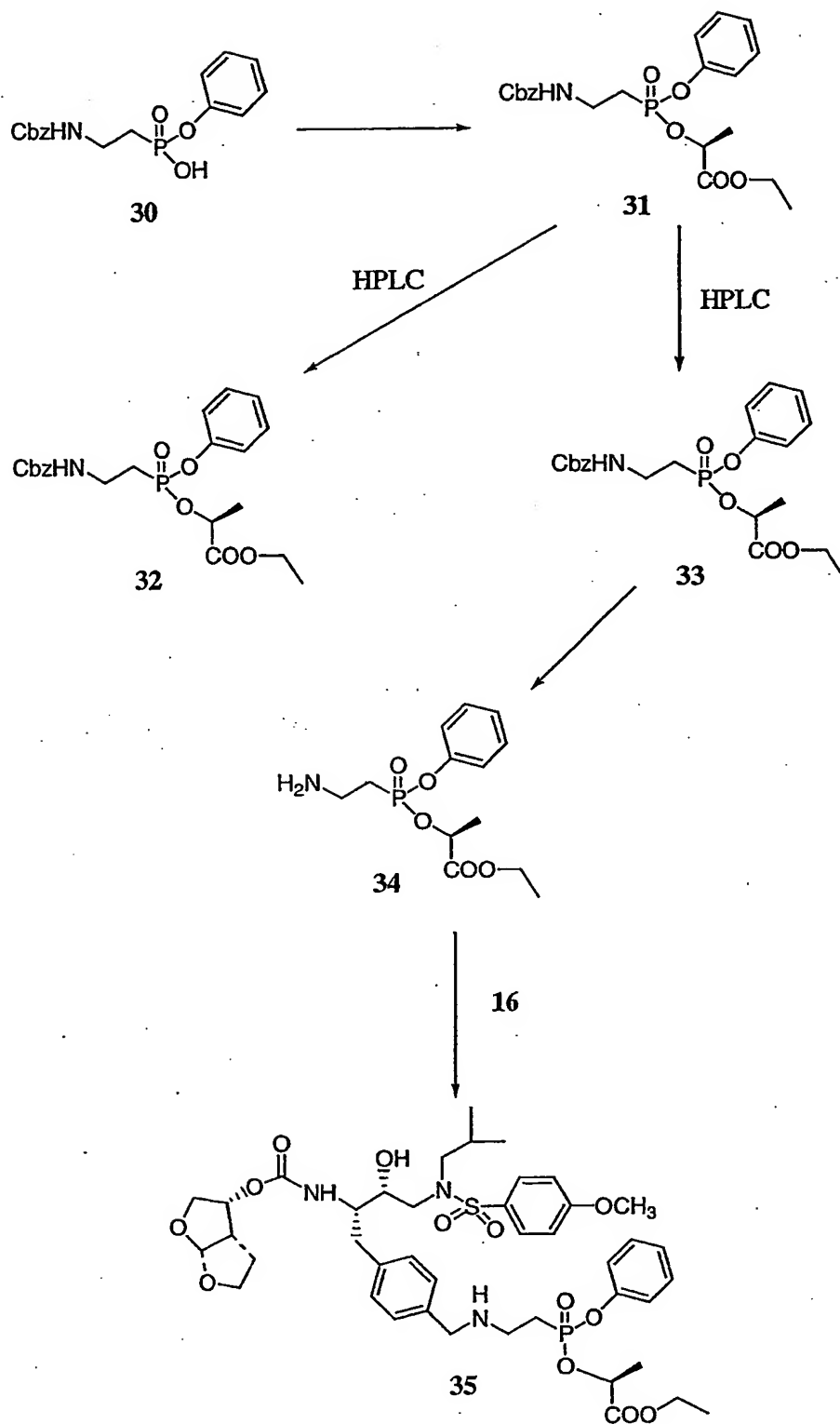
- 30 Compound 28: To a stirred solution of compound 16 (1.18 g, 2 mmol) in 9 mL of 1,2-dichloroethane was added compound 26 (830 mg, 2.2 mmol) and  $\text{MgSO}_4$  (80 mg), the resulted mixture was stirred at room temperature under argon for 3h, then acetic acid (0.34



mL, 6 mmol) and sodium cyanoborohydride (251mg, 4 mmol) were added. The reaction mixture was stirred at room temperature for 2 h under argon. Then aqueous NaHCO<sub>3</sub> (50 mL) was added, and the mixture was extracted with ethyl acetate, and the combined organic layers were washed with brine and water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOH/EtOAc, 1/9) to give 28 (880 mg, 50 %) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.71 (d, J = 8.7 Hz, 2H), 7.35-7.16 (m, 9H), 6.99 (d, J = 8.7 Hz, 2H), 5.64 (d, J = 5.4 Hz, 1H), 5.03-4.85 (m, 3H), 4.24-3.67 (m, overlapping s, 15H), 3.14-2.70 (m, 9H), 2.39-2.28 (m, 2H), 1.85-1.51 (m, 5H), 1.29-1.25 (m, 3H), 0.93-0.78 (m, 9H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 29.2; MS (ESI) 912 (M+Na).

#### Example 8F

Compound 29: To a stirred solution of compound 16 (857 g, 1.45 mmol) in 7 mL of 1,2-dichloroethane was added compound 27 (600 mg, 1.6 mmol) and MgSO<sub>4</sub> (60 mg), the resulted mixture was stirred at room temperature under argon for 3h, then acetic acid (0.23 mL, 3 mmol) and sodium cyanoborohydride (183mg, 2.9 mmol) were added. The reaction mixture was stirred at room temperature for 2 h under argon. Then aqueous NaHCO<sub>3</sub> (50 mL) was added, and the mixture was extracted with ethyl acetate, and the combined organic layers were washed with brine and water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOH/EtOAc, 1/9) to give 29 (650 mg, 50 %) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.72 (d, J = 8.7 Hz, 2H), 7.35-7.16 (m, 9H), 7.00 (d, J = 8.7 Hz, 2H), 5.64 (d, J = 5.4 Hz, 1H), 5.03-4.90 (m, 3H), 4.17-3.67 (m, overlapping s, 15H), 3.16-2.77 (m, 9H), 2.26-2.19 (m, 2H), 1.94-1.53 (m, 5H), 1.26-1.18 (m, 3H), 1.00-0.87 (m, 9H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 27.4; MS (ESI) 912 (M+Na).



Example 9A

Compound 31: To a stirred solution of compound 30 (20 g, 60 mmol) in 320 mL of toluene at room temperature under N<sub>2</sub> was added thionyl chloride (17.5 mL, 240 mmol) and a few drops of DMF. The resulted mixture was stirred at 60-70°C for 3 h. After cooled to room temperature, the solvent was removed under reduced pressure, and the residue was added 280 mL of DCM, followed by TEA (50 mL, 360 mmol) and (S) lactate ethyl ester (17 mL, 150 mmol). After 20h at room temperature, the solvent was removed under reduced pressure, and the residue was diluted with DCM and washed with brine and water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by chromatography on silica gel (DCM / EtOAc, 1:1) to give 31 (24 g, 92 %) as a yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.33-7.18 (m, 10H), 5.94-6.63 (m, 1H), 5.70 (m, 1H), 5.12-4.95 (m, 3H), 4.24-4.14 (m, 2H), 3.72-3.59(m, 2H), 2.35-2.20 (m, 2H), 1.58-1.19 (m, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 28.2 and 26.2; MS (ESI) 458 (M+Na).

15 Example 9B

Compound 32: Compound 31 was purified using a Dynamax SD-200 HPLC system. The mobile phase consisted of acetonitrile: water (60:40, v/v) at a flow rate of 70 mL/min. The injection volume was 3 mL. The detection was by fluorescence at 245 nm and peak area ratios were used for quantitations. Retention time was 8.1 min for compound 32 as yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.33-7.18 (m, 10H), 5.94-6.63 (m, 1H), 5.70 (m, 1H), 5.12-4.95 (m, 3H), 4.24-4.14 (m, 2H), 3.72-3.59(m, 2H), 2.35-2.20 (m, 2H), 1.58-1.19 (m, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 28.2; MS (ESI) 458 (M+Na).

Example 9C

25 Compound 33 was purified in the same manner and retention time was 7.9 min for compound 33 as yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.33-7.18 (m, 10H), 5.94-6.63 (m, 1H), 5.70 (m, 1H), 5.12-4.95 (m, 3H), 4.24-4.14 (m, 2H), 3.72-3.59(m, 2H), 2.35-2.20 (m, 2H), 1.58-1.19 (m, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 26.2; MS (ESI) 458 (M+Na).

30 Example 9D

Compound 34: A solution of compound 33 (3.2 g) was dissolved in 60 mL of EtOH, then 0.9 mL of acetic acid and 10 % Pd/C (640 mg) was added. The resulted mixture was stirred

under H<sub>2</sub> atmosphere (balloon) for 4 h. After filtration through celite, the filtered was evaporated under reduced pressure to afford the compound **34** (2.7 g, 99 %) as a colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.42-7.18 (m, 5H), 6.10 (s, 1H), 5.15-5.02 (m, 1H), 4.24-4.05 (m, 2H), 3.25-3.16 (m, 2H), 2.36-2.21 (m, 2H), 1.61-1.58 (m, 3H), 1.35- 1.18, m, 3H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 26.1; MS (ESI) 302 (M+1).

#### Example 9E

Compound **35**: To a stirred solution of compound **16** (8.9 g, 15 mmol) in 70 mL of 1,2-dichloroethane was added compound **34** (8.3 g, 23 mmol) and MgSO<sub>4</sub> (80 mg), the resulted mixture was stirred at room temperature under argon for 2.5h, then acetic acid (3 mL, 52.5 mmol) and sodium cyanoborohydride (1.9g, 30 mmol) were added. The reaction mixture was stirred at room temperature for 1.5 h under argon. Then aqueous NaHCO<sub>3</sub> (100 mL) was added, and the mixture was extracted with ethyl acetate, and the combined organic layers were washed with brine and water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOH/EtOAc, 1/9) to give **35** (8.4 g, 64 %) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.73 (d, J = 8.7 Hz, 2H), 7.36-7.17(m, 9H), 7.00 (d, J = 8.7 Hz, 2H), 5.64 (d, J = 5.1 Hz, 1H), 5.07-4.97 (m, 3H), 4.19 -3.67 (m overlapping s, 13H), 3.15-2.78 (m, 9H), 2.25-2.19 (m, 2H), 1.91-1.54 (m, 6H), 1.24-1.20 (m, 3H), 0.94-0.87 (m, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 27.4; MS (ESI) 876 (M+1).

#### Resolution of Compound 35 Diastereomers

Analysis was performed on an analytical Daicel Chiralcel OD column, conditions described below, with a total of about 3.5 mg compound **35** free base injected onto the column. This lot was about a 3:1 mixture of major to minor diastereomers where the lactate ester carbon is a 3:1 mix of R and S configurations.

Two injections of 3.8 and 3.5 mg each were made using the conditions described below. The isolated major diastereomer fractions were evaporated to dryness on a rotary evaporator under house vacuum. The chromatographic solvents were displaced by two portions of ethyl acetate followed by a single portion of ethyl acetate – trifluoroacetic acid (about 95:5) and a final high vacuum strip to aid in removal of trace solvents. This yielded the major diastereomer trifluoroacetate salt as a gummy solid.

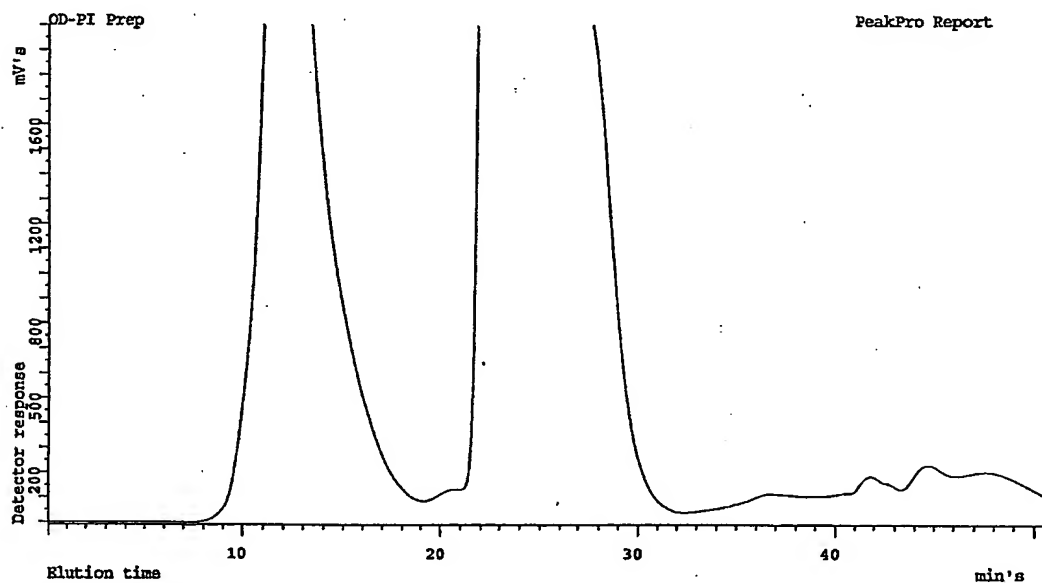
The resolved minor diastereomer was isolated for biological evaluation by an 11 mg injection, performed on an analytical Daicel Chiralcel OD column, using the conditions described in below. The minor diastereomer of 35 was isolated as the trifluoroacetate salt by the conditions described above.

5

Larger scale injections (~ 300 mg 35 per injection) were later performed on a Daicel Chiralcel OD column semi-preparative column with a guard column, conditions described below. A minimal quantity of isopropyl alcohol was added to heptane to dissolve the 3:1 diastereomeric mix of 35 and the resolved diastereomers sample, and the isolated fractions were refrigerated until the eluted mobile phase was stripped.

10

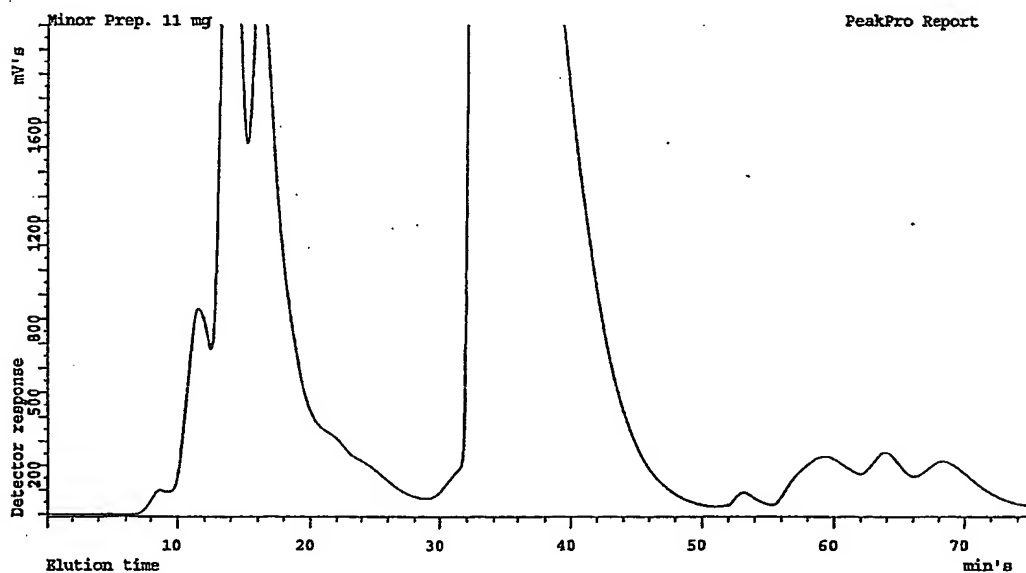
**Analytical Column, ~ 4 mg Injection, Heptane – EtOH (20:80) Initial**



15

**HPLC CONDITIONS**

Column : Chiralcel OD, 10  $\mu$ m, 4.6 x 250 mm  
Mobile Phase : Heptane – Ethyl Alcohol (20:80 initial)  
: 100% Ethyl Alcohol (final)  
**Note: Final began after first peak eluted**  
Flow Rate : 1.0 mL/min  
Run Time : As needed  
Detection : UV at 250 nm  
Temperature : Ambient  
Injection : ~ 4 mg on Column  
Sample Prep. : Dissolved in ~ 1 mL heptane –  
ethyl alcohol (50:50)  
Retention Times : 35 Minor ~ 14 min  
: 35 Major ~ 25 min

**Analytical Column, ~ 6 mg Injection, Heptane – EtOH (65:35) Initial**

**HPLC CONDITIONS**

Column : Chiralcel OD, 10  $\mu$ m, 4.6 x 250 mm

Mobile Phase : Heptane – Ethyl Alcohol (65:35 initial)  
: Heptane – Ethyl Alcohol (57.5:42.5 intermediate)  
Note: Intermediate began after impurity peaks eluted  
: Heptane – Ethyl Alcohol (20:80 final)  
Note: Final mobile phase began after minor  
diastereomer eluted

Flow Rate : 1.0 mL/min

Run Time : As needed

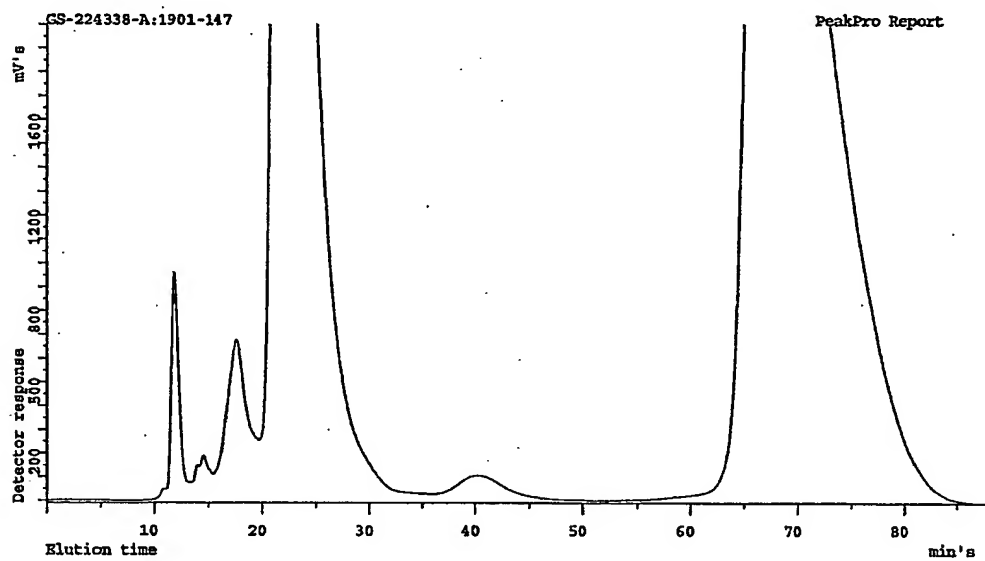
Detection : UV at 250 nm

Temperature : Ambient

Injection : ~ 4 mg on Column

Sample Prep. : Dissolved in ~ 1 mL heptane –  
ethyl alcohol (50:50)

Retention Times : 35 Minor ~ 14 min  
: 35 Major ~ 40 min

**Semi-Preparative Column, ~ 300 mg Injection, Heptane – EtOH (65:35) Initial**



**HPLC CONDITIONS**

Columns : Chiralcel OD, 20  $\mu$ m, 21 x 50 mm (guard)  
: Chiralcel OD, 20  $\mu$ m, 21 x 250 mm

Mobile Phase : Heptane – Ethyl Alcohol (65:35 initial)  
: Heptane – Ethyl Alcohol (50:50 intermediate)  
Note: Intermediate began after minor  
diastereomer peak eluted  
: Heptane – Ethyl Alcohol (20:80 final)  
Note: Final mobile phase began after major  
diastereomer began to elute

Flow Rate : 10.0 mL/min

Run Time : As needed

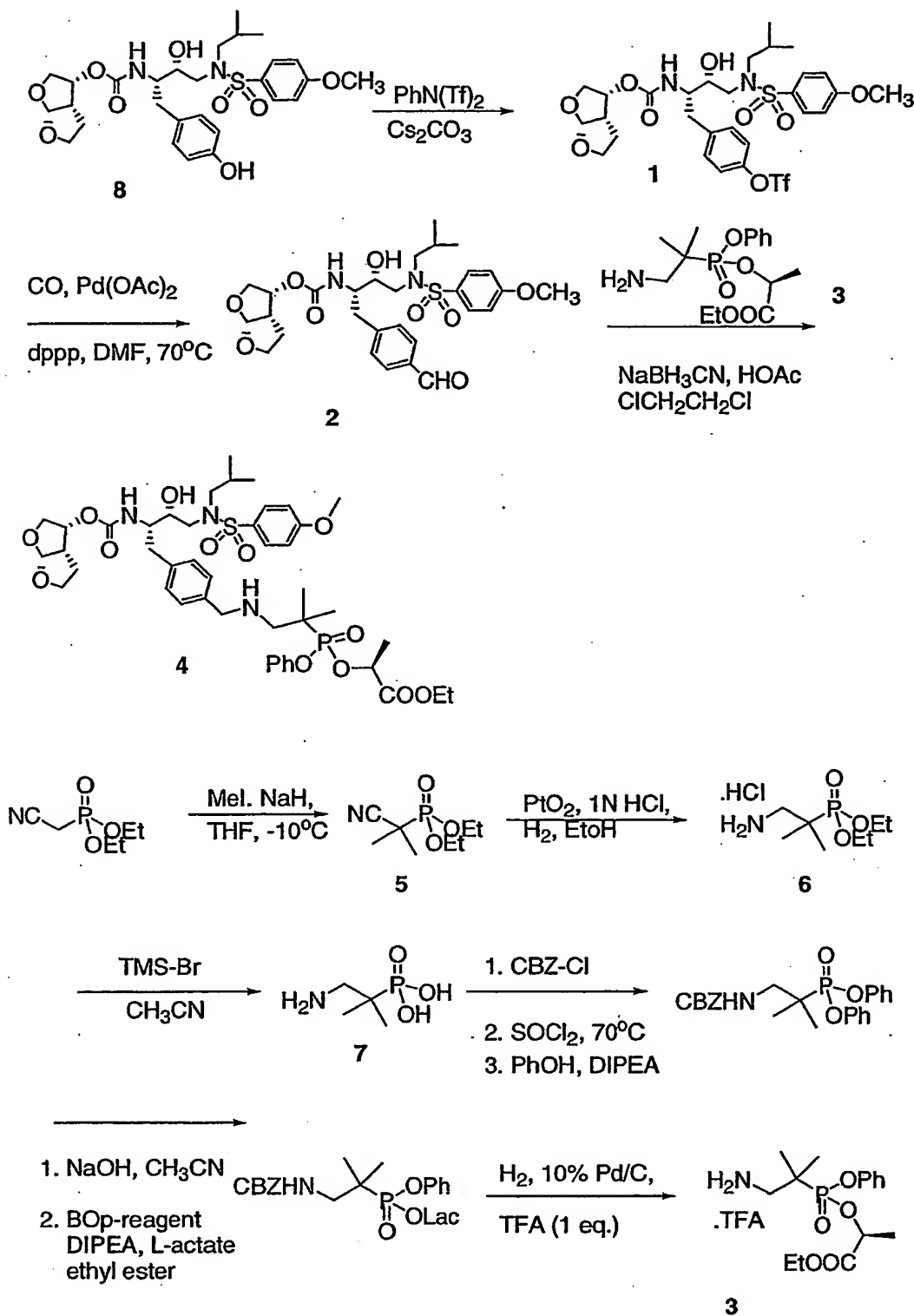
Detection : UV at 260 nm

Temperature : Ambient

Injection : ~ 300 mg on Column

Sample Prep. : Dissolved in ~ 3.5 mL heptane –  
ethyl alcohol (70:30)

Retention Times : 35 Minor ~ 14 min  
: 35 Major ~ 40 min



Example 29

Triflate derivative 1: A THF-CH<sub>2</sub>Cl<sub>2</sub> solution (30mL-10 mL) of 8 (4 g, 6.9 mmol), cesium carbonate (2.7 g, 8 mmol), and N-phenyltrifluoromethane sulfonimide (2.8 g, 8 mmol) was reacted overnight. The reaction mixture was worked up, and concentrated to dryness to give  
5 crude triflate derivative 1.

Aldehyde 2: Crude triflate 1 (4.5 g, 6.9 mmol) was dissolved in DMF (20 mL), and the solution was degassed (high vacuum for 2 min, Ar purge, repeat 3 times). Pd(OAc)<sub>2</sub> (0.12 g, 0.27 mmol), and bis(diphenylphosphino)propane (dppp, 0.22 g, 0.27 mmol) were added, the  
10 solution was heated to 70°C. Carbon monoxide was rapidly bubbled through the solution, then under 1 atmosphere of carbon monoxide. To this solution were slowly added TEA (5.4 mL, 38 mmol), and triethylsilane (3 mL), 18 mmol). The resulting solution was stirred overnight at room temperature. The reaction mixture was worked up, and purified on silica gel column chromatograph to afford aldehyde 2 (2.1 g, 51 %). (Hostetler, et al J. Org. Chem.,  
15 1999, 64, 178-185).

Lactate prodrug 4: Compound 4 is prepared as described above procedure for Example 9B, Compound 35 by the reductive amination between 2 and 3 with NaBH<sub>3</sub>CN in 1,2-dichloroethane in the presence of HOAc.  
20

Example 30 Preparation of Compound 3

Diethyl (cyano(dimethyl)methyl) phosphonate 5: A THF solution (30 mL) of NaH (3.4 g of 60% oil dispersion, 85 mmol) was cooled to -10°C, followed by the addition of diethyl (cyanomethyl)phosphonate (5g, 28.2 mmol) and iodomethane (17 g, 112 mmol). The  
25 resulting solution was stirred at -10°C for 2 hr, then 0°C for 1 hr, was worked up, and purified to give dimethyl derivative 5 (5 g, 86 %).

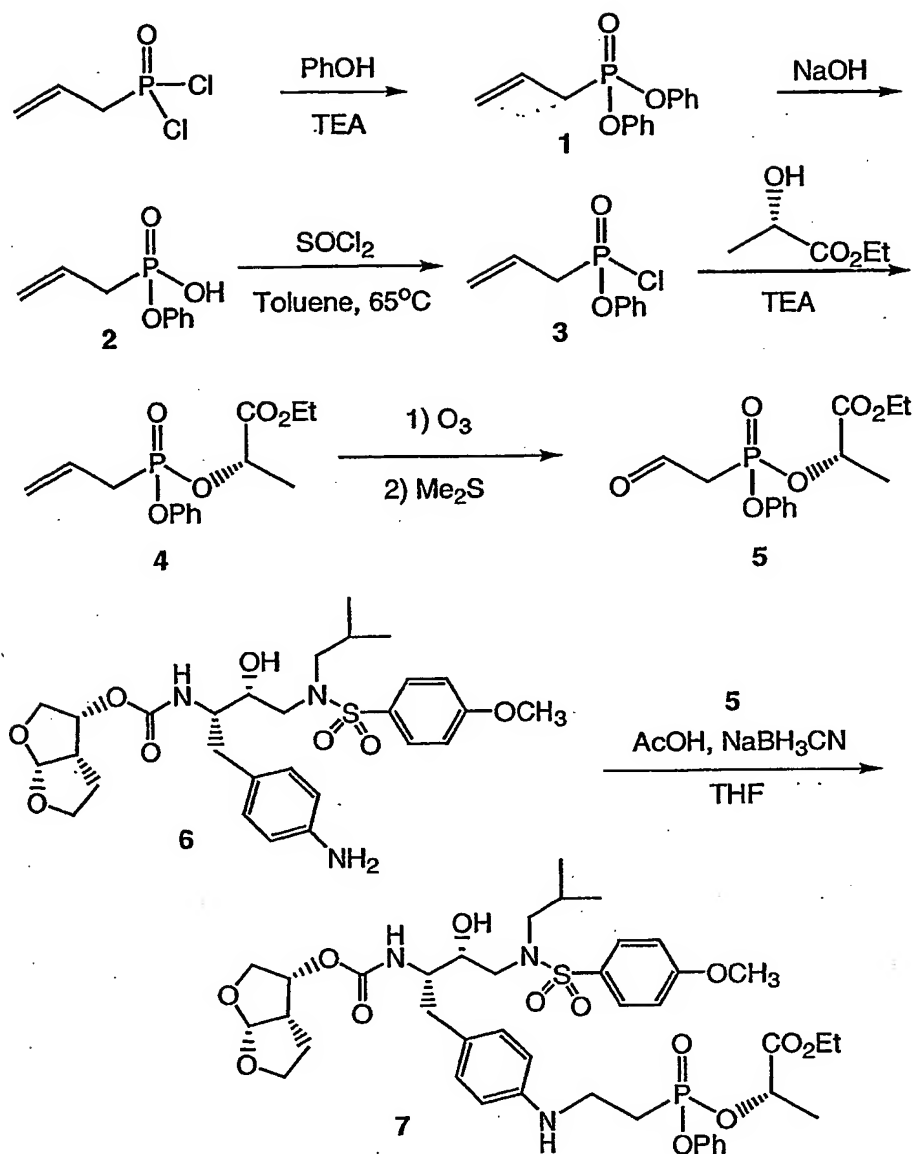
Diethyl (2-amino-1,1-dimethyl-ethyl)phosphonate 6: Compound 5 was reduced to amine derivative 6 by the described procedure (J. Med. Chem. 1999, 42, 5010-5019).

A solution of ethanol (150 mL) and 1N HCl aqueous solution (22 mL) of 5 (2.2 g, 10.7  
30 mmol) was hydrogenated at 1 atmosphere in the presence of PtO<sub>2</sub> (1.25 g) at room temperature overnight. The catalyst was filtered through a celite pad. The filtrate was concentrated to dryness, to give crude 6 (2.5g, as HCl salt).

2-Amino-1,1-dimethyl-ethyl phosphonic acid 7: A solution of CH<sub>3</sub>CN (30 mL) of crude 6 (2.5 g) was cooled to 0°C, and treated with TMSBr (8 g, 52 mmol) for 5 hr. The reaction mixture was stirred with methanol for 1.5 hr at room temperature, concentrated, recharged with methanol, concentrated to dryness to give crude 7 which was used for next reaction without further purification.

Lactate phenyl (2-amino-1,1-dimethyl-ethyl)phosphonate 3: Compound 3 is synthesized according to the procedures described in Example 9D, Compound 34 for the preparation of lactate phenyl 2-aminoethyl phosphonate 34. Compound 7 is protected with CBZ, followed by the reaction with thionyl chloride at 70°C. The CBZ protected dichlorodate is reacted phenol in the presence of DIPEA. Removal of one phenol, follow by coupling with ethyl L-lactate leads N-CBZ-2-amino-1,1-dimethyl-ethyl phosphonate derivative. Hydrogenation of N-CBZ derivative at 1 atmosphere in the presence of 10 % Pd/C and 1 eq. of TFA affords compound 3 as TFA salt.

Scheme 1

5 Example 1

Monophenol Allylphosphonate 2: To a solution of allylphosphonic dichloride (4 g, 25.4 mmol) and phenol (5.2 g, 55.3 mmol) in  $\text{CH}_2\text{Cl}_2$  (40 mL) at  $0^\circ\text{C}$  was added TEA (8.4 mL, 60 mmol). After stirred at room temperature for 1.5 h, the mixture was diluted with hexane-ethyl acetate and washed with HCl (0.3 N) and water. The organic phase was dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The residue was filtered through a pad of silica gel (eluted with 2:1 hexane-ethyl acetate) to afford crude product diphenol

allylphosphonate 1 (7.8 g, containing the excessive phenol) as an oil which was used directly without any further purification. The crude material was dissolved in CH<sub>3</sub>CN (60 mL), and NaOH (4.4N, 15 mL) was added at 0°C. The resulted mixture was stirred at room temperature for 3 h, then neutralized with acetic acid to pH = 8 and concentrated under reduced pressure to remove most of the acetonitrile. The residue was dissolved in water (50 mL) and washed with CH<sub>2</sub>Cl<sub>2</sub> (3X25 mL). The aqueous phase was acidified with concentrated HCl at 0°C and extracted with ethyl acetate. The organic phase was dried over MgSO<sub>4</sub>, filtered, evaporated and co-evaporated with toluene under reduced pressure to yield desired monophenol allylphosphonate 2 (4.75 g, 95%) as an oil.

### Example 2

Monolactate Allylphosphonate 4: To a solution of monophenol allylphosphonate 2 (4.75 g, 24 mmol) in toluene (30 mL) was added SOCl<sub>2</sub> (5 mL, 68 mmol) and DMF (0.05 mL). After stirred at 65°C for 4 h, the reaction was completed as shown by <sup>31</sup>P NMR. The reaction mixture was evaporated and co-evaporated with toluene under reduced pressure to give monochloride 3 (5.5 g) as an oil. To a solution of chloride 3 in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) at 0°C was added ethyl (s)-lactate (3.3 mL, 28.8 mmol), followed by TEA. The mixture was stirred at 0°C for 5 min then at room temperature for 1 h, and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and HCl (0.2N), the organic phase was washed with water, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford desired monolactate 4 (5.75 g, 80%) as an oil (2:1 mixture of two isomers): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.1-7.4 (m, 5H), 5.9 (m, 1H), 5.3 (m, 2H), 5.0 (m, 1H), 4.2 (m, 2H), 2.9 (m, 2H), 1.6; 1.4 (d, 3H), 1.25 (m, 3H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 25.4, 23.9.

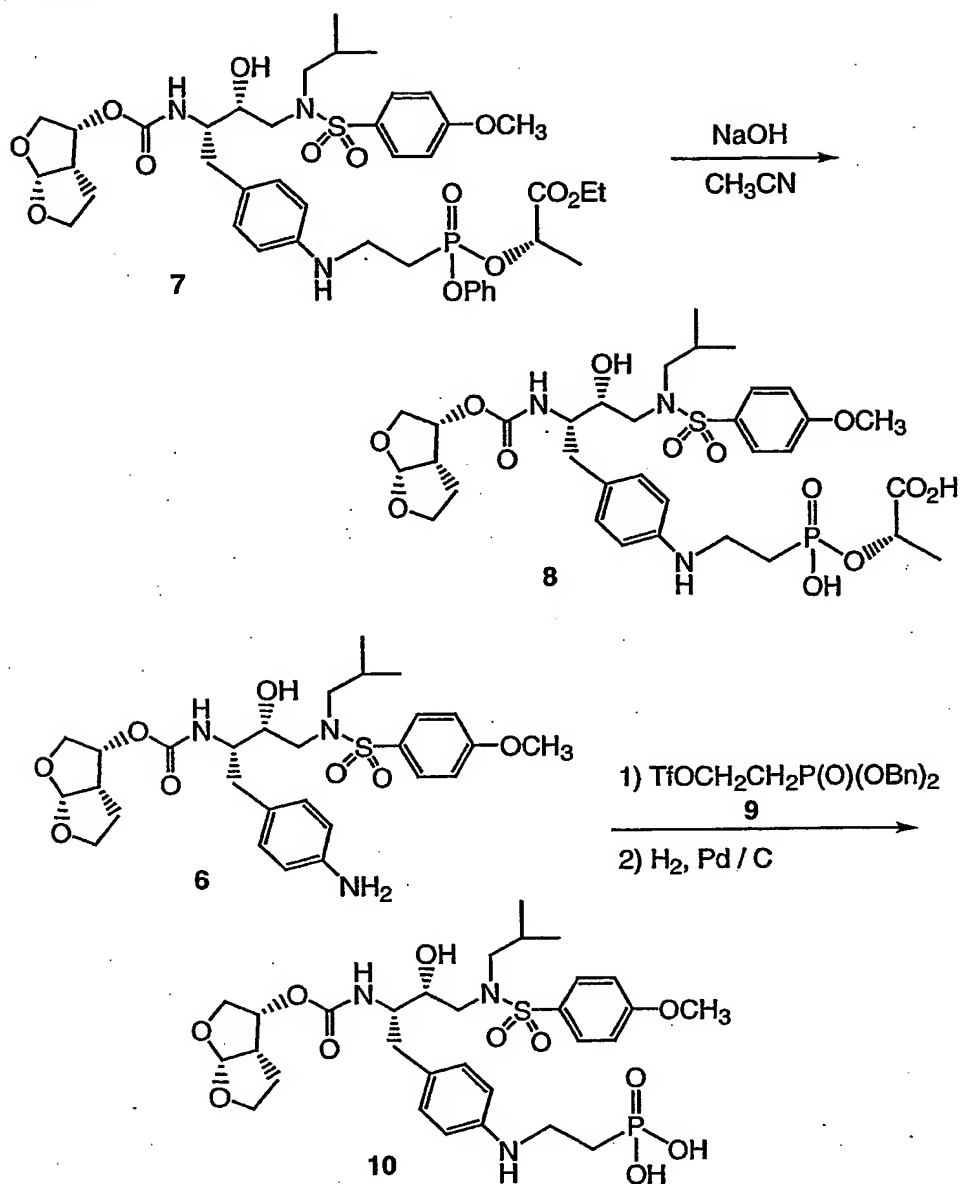
### Example 3

Aldehyde 5: A solution of allylphosphonate 4 (2.5 g, 8.38 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) was bubbled with ozone air at -78°C until the solution became blue, then bubbled with nitrogen until the blue color disappeared. Methyl sulfide (3 mL) was added at -78°C. The mixture was warmed up to room temperature, stirred for 16 h and concentrated under reduced pressure to give desired aldehyde 5 (3.2 g, as a 1:1 mixture of DMSO): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.8 (m, 1H), 7.1-7.4 (m, 5H), 5.0 (m, 1H), 4.2 (m, 2H), 3.4 (m, 2H), 1.6; 1.4 (d, 3H), 1.25 (m, 3H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 17.7, 15.4.

Example 4

Compound 7: To a solution of aniline 6 (reported before) (1.62 g, 2.81 mmol) in THF (40 mL) was added acetic acid (0.8 mL, 14 mmol), followed by aldehyde 5 (1.3 g, 80%, 3.46 mmol) and  $\text{MgSO}_4$  (3 g). The mixture was stirred at room temperature for 0.5 h, then  $\text{NaBH}_3\text{CN}$  (0.4 g, 6.37 mmol) was added. After stirred for 1 h, the reaction mixture was filtered. The filtrate was diluted with ethyl acetate and washed with  $\text{NaHCO}_3$ , dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to give compound 6 (1.1g, 45%) as a 3:2 mixture of two isomers, which were separated by HPLC (mobile phase, 70%  $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ ; flow rate: 70 mL/min; detection: 254 nm; column: 8 $\mu$  C18, 41X250 mm, Varian). Isomer A (0.39 g):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.75 (d, 2H), 7.1-7.4 (m, 5H), 7.0 (m, 4H), 6.6 (d, 2H), 5.65 (d, 1H), 5.05 (m, 2H), 4.9 (d, 1H), 4.3 (brs, 1H), 4.2 (q, 2H), 3.5-4.0 (m, 6H), 3.9 (s, 3H), 2.6-3.2 (m, 9H), 2.3 (m, 2), 1.6-1.9 (m, 5H), 1.25 (t, 3H), 0.9 (2d, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  26.5; MS (ESI): 862 (M+H). Isomer B (0.59 g):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.75 (d, 2H), 7.1-7.4 (m, 5H), 7.0 (m, 4H), 6.6 (d, 2H), 5.65 (d, 1H), 5.05 (m, 2H), 4.9 (d, 1H), 4.5 (brs, 1H), 4.2 (q, 2H), 3.5-4.0 (m, 6H), 3.9 (s, 3H), 2.7-3.2 (m, 9H), 2.4 (m, 2), 1.6-1.9 (m, 2H), 1.4 (d, 3H), 1.25 (t, 3H), 0.9 (2d, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  28.4; MS (ESI): 862 (M+H).

Scheme 2

**Example 5**

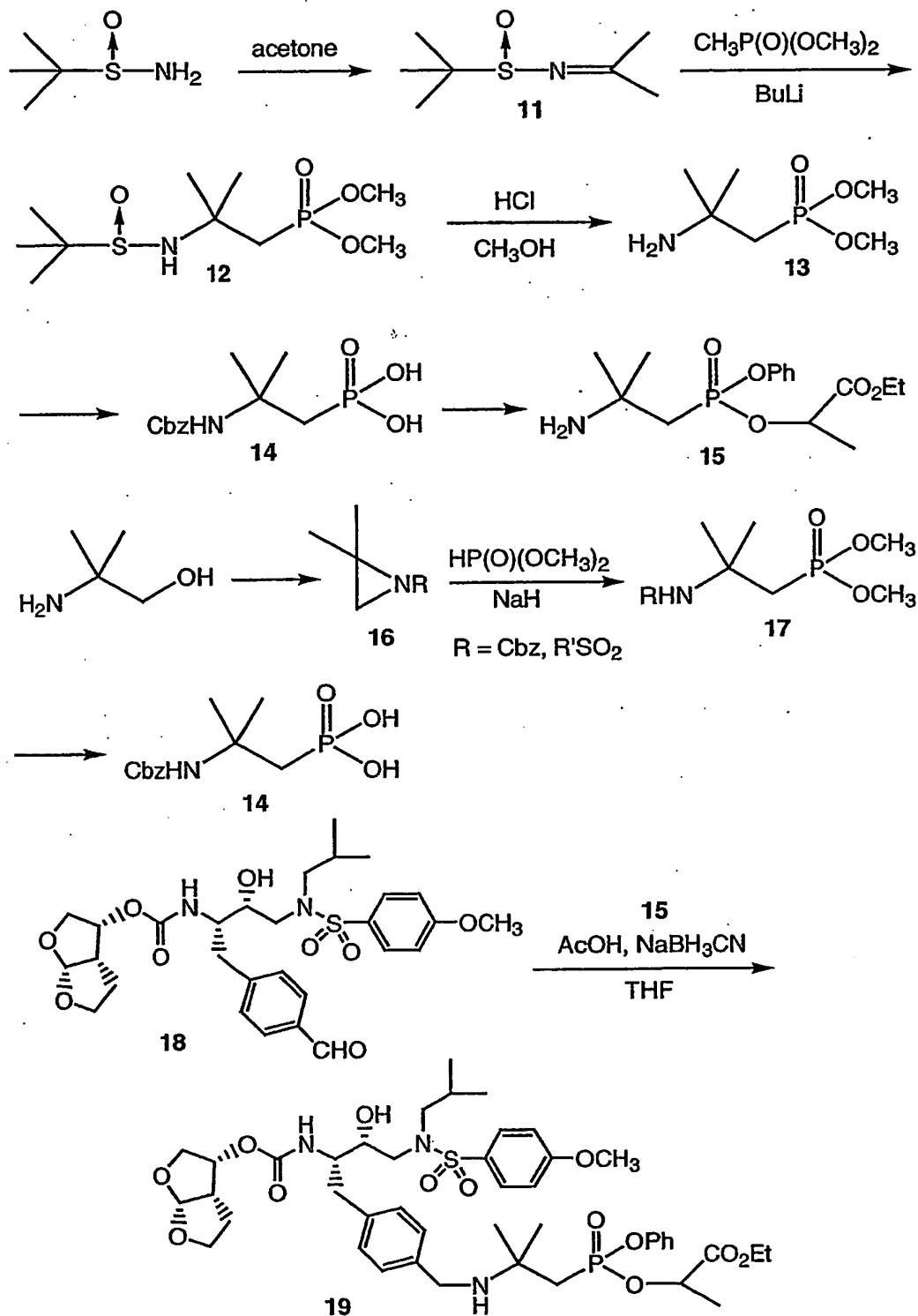
- 5 Acid 8: To a solution of compound 7 (25 mg, 0.029 mmol) in acetonitrile (1 mL) at 0°C was added NaOH (1N, 0.125 mL). The mixture was stirred at 0°C for 0.5 h and at room temperature for 1 h. The reaction was quenched with acetic acid and purified by HPLC to give acid 8 (10 mg, 45%). <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.8 (d, 2H), 7.5 (d, 2H), 7.4 (d, 2H), 7.1 (d, 2H), 5.6 (d, 1H), 4.9 (m, 3H), 3.2-4.0 (m, 6H), 3.9 (s, 3H), 2.6-3.2 (m, 9H), 2.05 (m, 2), 1.4-
- 10 1.7 (m, 2H), 1.5 (d, 3H), 0.9 (2d, 6H); <sup>31</sup>P NMR (CD<sub>3</sub>OD) δ 20.6; MS (ESI): 758 (M+H).



Example 6

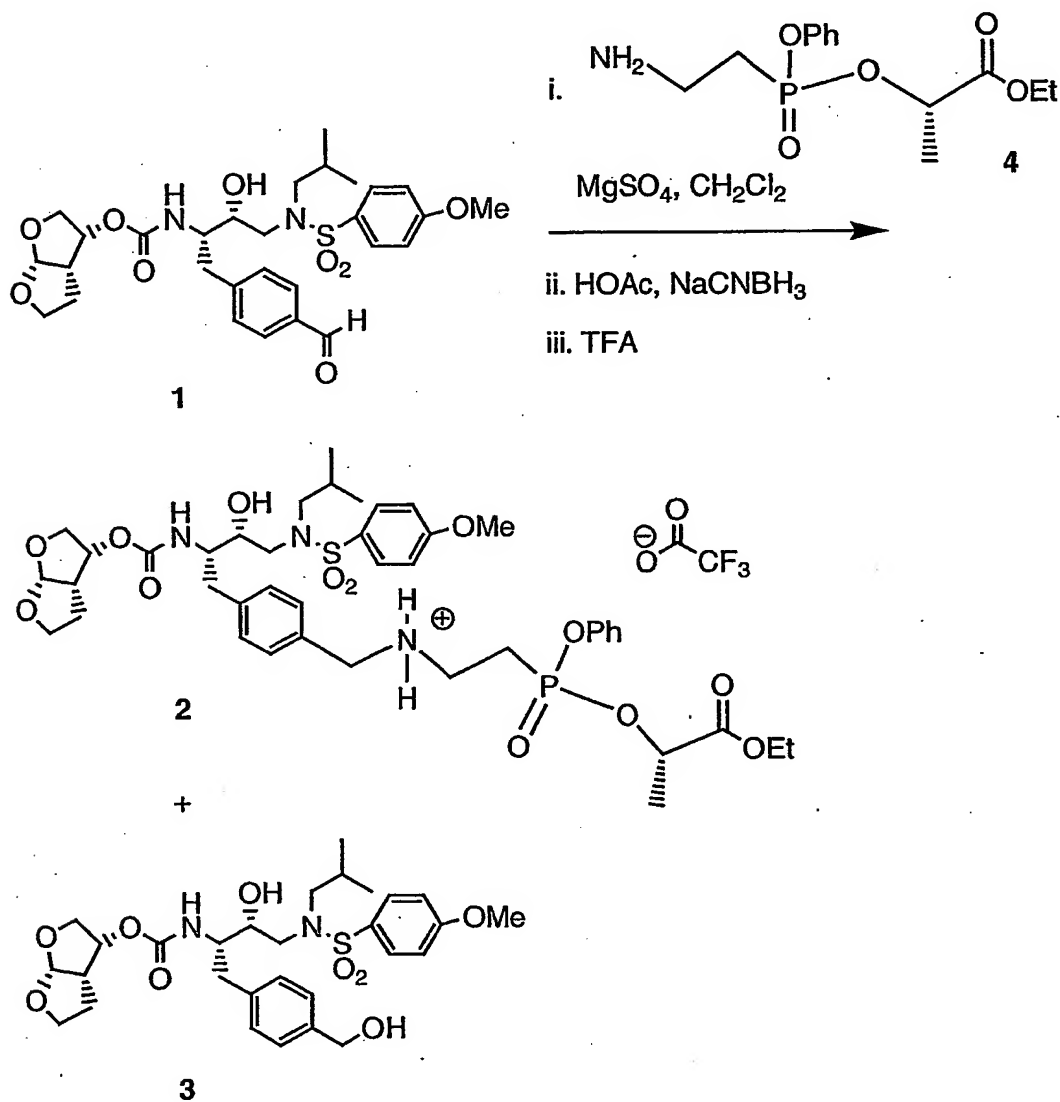
Diacid 10: To a solution of triflate 9 (94 mg, 0.214 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added a solution of aniline 6 (100 mg, 0.173 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) at -40°C, followed by 2,6-lutidine (0.026 mL). The mixture was warmed up to room temperature and stirred for 1 h. Cesium carbonate (60 mg) was added and the reaction mixture was stirred for additional 1 h. The mixture was diluted with ethyl acetate, washed with HCl (0.2N), dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by HPLC to afford dibenzyl phosphonate (40 mg). To a solution of this dibenzyl phosphonate in ethanol (3 mL) and ethyl acetate (1 mL) was added 10% Pd/C (40 mg). The mixture was stirred under hydrogen atmosphere (balloon) for 4 h. The reaction mixture was diluted with methanol, filtered and concentrated under reduced pressure. The residue was washed with ethyl acetate and dried to give desired product diacid 10 (20 mg). <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.8 (d, 2H), 7.3 (d, 2H), 7.1 (2d, 4H), 5.6 (d, 1H), 4.9 (m, 2H), 3.4-4.0 (m, 6H), 3.9 (s, 3H), 2.5-3.2 (m, 9H), 2.0 (m, 2), 1.4-1.7 (m, 2H), 0.9 (2d, 6H); <sup>31</sup>P NMR (CD<sub>3</sub>OD) δ 22.1; MS (ESI): 686 (M+H).

### Scheme 3



The synthesis of compound **19** is outlined in Scheme 3. Condensation of 2-methyl-2-propanesulfonamide with acetone give sulfinyl imine **11** (J. Org. Chem. 1999, 64, 12).

- Addition of dimethyl methylphosphonate lithium to **11** afford **12**. Acidic methanolysis of **12** provide amine **13**. Protection of amine with Cbz group and removal of methyl groups yield phosphonic acid **14**, which can be converted to desired **15** using methods reported earlier on. An alternative synthesis of compound **14** is also shown in Scheme 3. Commercially available
- 5 2-amino-2-methyl-1-propanol is converted to aziridines **16** according to literature methods (J. Org. Chem. 1992, 57, 5813; and Syn. Lett. 1997, 8, 893). Aziridine opening with phosphite give **17** (Tetrahedron Lett. 1980, 21, 1623). Deprotection (and, if necessary, reprotection) of **17** afford **14**. Reductive amination of amine **15** and aldehyde **18** provides compound **19**.



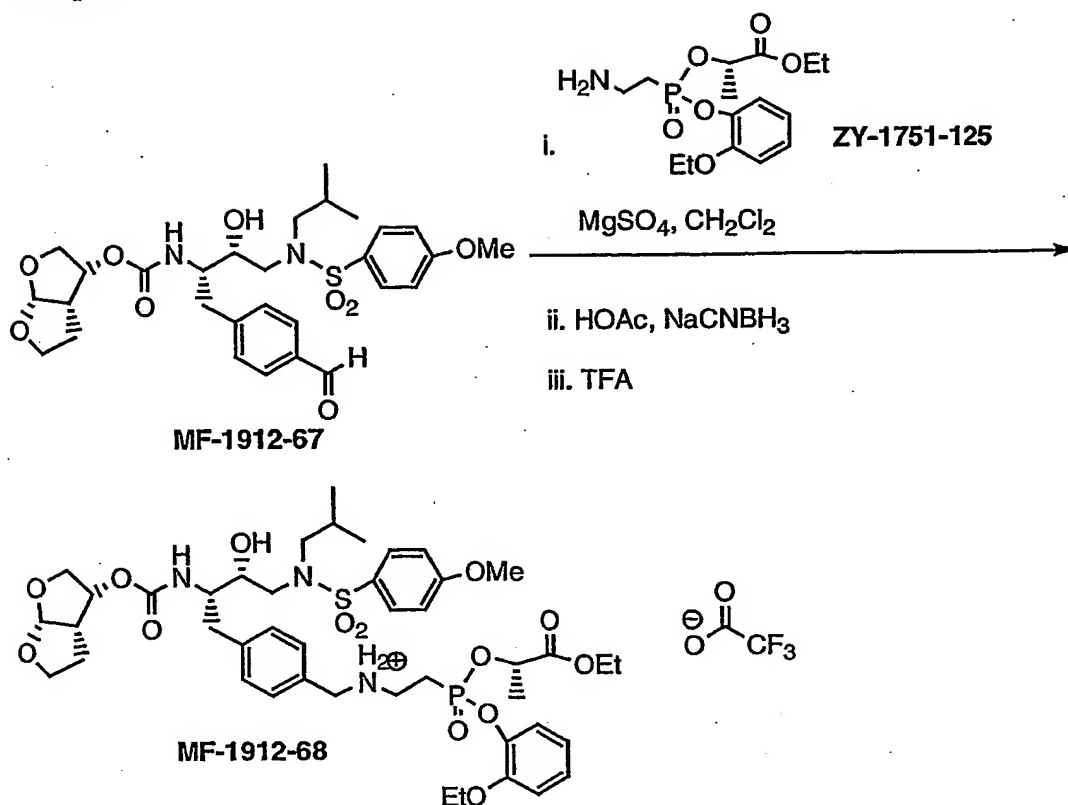
Example 1

2- $\{[2-(4-\{2-(\text{Hexahydro-furo}[2,3-b]\text{furan-3-yloxycarbonylamino})-3\text{-hydroxy-4-[isobutyl-(4-methoxy-benzenesulfonyl)-amino]-butyl}-\text{benzylamino})\text{-ethyl]-phenoxy-phosphinoyloxy}\}$ -propionic acid ethyl ester 2 (Compound 35, previous Example 9E).

5

A solution of 1 (2.07 g, 3.51 mmol) and 4 (1.33 g, 3.68 mmol of a 4:1 mixture of two diastereomers at the phosphorous center) were dissolved in 14 mL of  $(\text{CH}_2\text{Cl}_2)_2$  to provide a clear solution. Addition of  $\text{MgSO}_4$  (100 mg) to the solution resulted in a white cloudy mixture. The solution was stirred at ambient temperature for 3 hours when acetic acid (0.80 mL, 14.0 mmol) and sodium cyanoborohydride (441 mg, 7.01 mmol) were added. Following the reaction progress by TLC showed complete consumption of the aldehyde starting materials in 1 hour. The reaction mixture was worked up by addition of 200 mL of saturated aqueous  $\text{NaHCO}_3$  and 400 mL of  $\text{CH}_2\text{Cl}_2$ . The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  two more times (2 x 300 mL). The combined organic extracts were dried *in vacuo* and purified by column chromatography (EtOAc- 10% MeOH: EtOAc) to provide the desired product as a foam. The early eluting compound from the column was collected and characterized as alcohol 3 (810 mg, 39%). Addition of TFA (3 x 1 mL) generated the TFA salt which was lyophilized from 50 mL of a 1:1  $\text{CH}_3\text{CN}:\text{H}_2\text{O}$  to provide 1.63 g (47%) of the product 2 as a white powder.  $^1\text{H}$  NMR ( $\text{CD}_3\text{CN}$ )  $\delta$  8.23 (br s, 2H), 7.79 (d,  $J=8.4$  Hz, 2H), 7.45- 7.13 (m, 9H), 7.09 (d,  $J=8.4$  Hz, 2H), 5.86 (d,  $J=9.0$  Hz, 1H), 5.55 (d,  $J=4.8$  Hz, 1H), 5.05-4.96 (m, 1H), 4.96- 4.88 (m, 1H), 4.30-4.15 (m, 4H), 3.89 (s, 3H), 3.86- 3.76 (m, 4H), 3.70- 3.59 (m, 4H), 3.56- 3.40 (m, 2H), 3.34 (d,  $J=15$  Hz, 1H), 3.13 (d,  $J=13.5$  Hz, 1H), 3.06- 2.93 (m, 2H), 2.92- 2.80 (m, 2H), 2.69- 2.43 (m, 3H), 2.03- 1.86 (m, 1H), 1.64- 1.48 (m, 1H), 1.53 and 1.40 (d,  $J=6.3$  Hz,  $J=6.6$  Hz, 3H), 1.45- 1.35 (m, 1H), 1.27 and 1.23 (t,  $J=6.9$  Hz,  $J=7.2$  Hz, 3H), 0.90 (t,  $J=6.9$  Hz, 6H).  $^{31}\text{P}$  NMR ( $\text{CD}_3\text{CN}$ )  $\delta$  24.47, 22.86. ESI ( $\text{M}^+ \text{H}^+$ ) 876.4.

25

Example 2

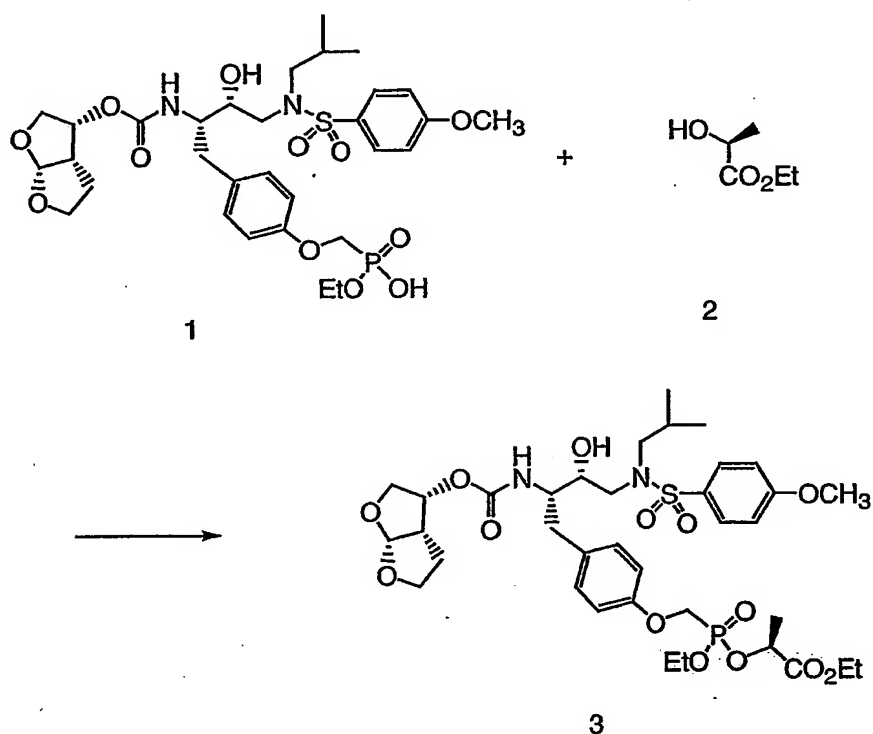
2-[[2-(4-{2-(Hexahydro-furo[2,3-b]furan-3-yloxycarbonylamino)-3-hydroxy-4-[isobutyl-(4-methoxy-benzenesulfonyl)-amino]-butyl}-benzylamino)-ethyl]-phenoxy-phosphinyloxy]-propionic acid ethyl ester (**MF-1912-68**):

A solution of **MF-1912-67** (0.466 g, 0.789 mmol) and **ZY-1751-125** (0.320 g, 0.789 mmol of a 1:1 mixture of two diastereomers at the phosphorous center) were dissolved in 3.1 mL of  $(\text{CH}_2\text{Cl}_2)_2$  to provide a clear solution. Addition of  $\text{MgSO}_4$  (20 mg) to the solution resulted in a white cloudy mixture. The solution was stirred at ambient temperature for 3 hours when acetic acid (0.181 mL, 3.16 mmol) and sodium cyanoborohydride (99 mg, 1.58 mmol) were added. Following the reaction progress by TLC showed complete consumption of the aldehyde starting materials in 1.5 hour. The reaction mixture was worked up by addition of 50 mL of saturated aqueous  $\text{NaHCO}_3$  and 200 mL of  $\text{CH}_2\text{Cl}_2$ . The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  two more times (2 x 200 mL). The combined organic extracts were dried *in vacuo* and purified by column chromatography (EtOAc- 10% MeOH: EtOAc) to provide the desired product as a foam. The early eluting compound from the column was collected and characterized to be MF-1912-48b alcohol (190 mg, 41%): Addition of TFA (3 x 1 mL) generated the TFA salt which was lyophilized from 50 mL of a 1:1  $\text{CH}_3\text{CN}$ :  $\text{H}_2\text{O}$  to

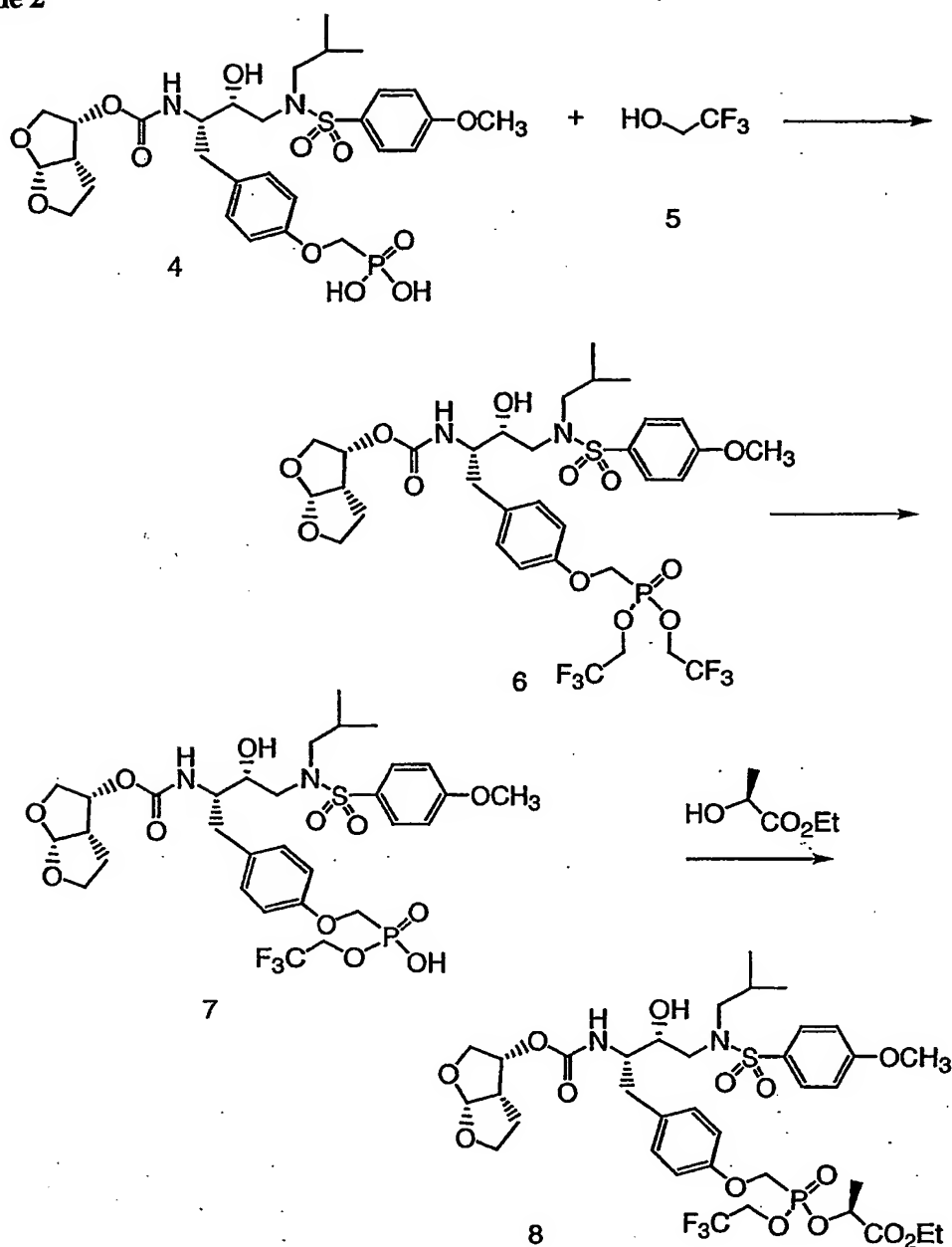
provide 0.389 g (48%) of the product as a white powder.  $^1\text{H}$  NMR ( $\text{CD}_3\text{CN}$ )  $\delta$  8.39 (br s, 2H), 7.79 (d,  $J=8.7$  Hz, 2H), 7.40 (d,  $J=7.5$  Hz, 2H), 7.34 (d,  $J=8.1$  Hz, 2H), 7.26-7.16 (m, 2H), 7.10 (d,  $J=9$  Hz, 3H), 7.01- 6.92 (m, 1H), 5.78 (d,  $J=9.0$  Hz, 1H), 5.55 (d,  $J=5.1$  Hz, 1H), 5.25-5.03 (m, 1H), 4.95- 4.88 (m, 1H), 4.30- 4.17 (m, 4H), 4.16- 4.07 (m, 2H), 3.90 (s, 3H), 3.88-3.73 (m, 4H), 3.72- 3.60 (m, 2H), 3.57- 3.38 (m, 2H), 3.32 (br d,  $J=15.3$  Hz, 1H), 3.13 (br d,  $J=14.7$  Hz, 1H), 3.05- 2.92 (m, 2H), 2.92- 2.78 (m, 2H), 2.68- 2.48 (m, 3H), 2.03- 1.90 (m, 1H), 1.62- 1.51 (m, 1H), 1.57 and 1.46 (d,  $J=6.9$  Hz,  $J=6.9$  Hz, 3H), 1.36- 1.50 (m, 1H), 1.43- 1.35 (m, 4H), 1.33- 1.22 (m, 3H), 0.91 (t,  $J=6.6$  Hz, 6H).  $^{31}\text{P}$  NMR ( $\text{CD}_3\text{CN}$ )  $\delta$  25.27, 23.56. ESI ( $\text{M}+\text{H}$ ) $^+$  920.5.

10

Scheme 1



Scheme 2

Example 1

- 5 Mono-Ethyl mono-lactate 3: To a solution of 1 (96mg, 0.137 mmol) and ethyl lactate 2 (0.31 mL, 2.7 mmol) in pyridine (2 mL) was added N, N-dicyclohexylcarbodiimide (170 mg, 0.822 mmol). The solution was stirred for 18h at 70°C. The mixture was cooled to room temperature and diluted with dichloromethane. The solid was removed by filtration and the filtrate was concentrated. The residue was suspended in diethyl ether/dichloromethane and

filtered again. The filtrate was concentrated and mixture was chromatographed on silica gel eluting with EtOAc/hexane to provide compound 3 (43 mg, 40%) as a foam:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71 (d, 2H), 7.00 (d, 2H); 7.00 (d, 2H), 6.88 (d, 2H), 5.67 (d, 1H), 4.93-5.07 (m, 2H), 4.15-4.39 (m, 6H), 3.70-3.99 (m, 10H), 2.76-3.13 (m, 7H), 1.55-1.85 (m, 9H), 1.23-1.41 (m, 6H), 0.90 (dd, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.1, 20.2; MS (ESI) 823 (M+Na).

#### Example 2

Bis-2,2,2-trifluoroethyl phosphonate 6: To a solution of 4 (154mg, 0.228 mmol) and 222,-trifluoroethanol 5 (1 mL, 13.7 mmol) in pyridine (3 mL) was added N, N-dicyclohexylcarbodiimide (283 mg, 1.37 mmol). The solution was stirred for 6.5h at 70°C. The mixture was cooled to room temperature and diluted with dichloromethane. The solid was removed by filtration and the filtrate was concentrated. The residue was suspended in dichloromethane and filtered again. The filtrate was concentrated and mixture was chromatographed on silica gel eluting with EtOAc/hexane to provide compound 6 (133 mg, 70%) as a foam:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71 (d, 2H), 7.21 (d, 2H); 7.00 (d, 2H), 6.88 (dd, 2H), 5.66 (d, 1H), 4.94-5.10 (m, 3H), 4.39-4.56 (m, 6H), 3.71-4.00 (m, 10H), 2.77-3.18 (m, 7H), 1.67-1.83(m, 2H), 0.91 (dd, 4H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  22.2; MS (ESI) 859 (M+Na).

#### Example 3

Mono-2,2,2-trifluoroethyl phosphonate 7: To a solution of 6 (930mg, 1.11 mmol) in THF (14 mL) and water (10 mL) was added an aqueous solution of NaOH in water (1N, 2.2 mL). The solution was stirred for 1h at 0°C. An excess amount of Dowex resin ( $\text{H}^+$ ) was added to until pH=1. The mixture was filtered and the filtrate was concentrated under reduced pressure. The concentrated solution was azeotroped with EtOAc/toluene three times and the white powder was dried *in vacuo* provide compound 7 (830 mg, 100%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71 (d, 2H), 7.11 (d, 2H); 6.99 (d, 2H), 6.85 (d, 2H), 5.63 (d, 1H), 5.26 (m, 1H), 5.02 (m, 1H), 4.40 (m, 1H), 4.14 (m, 4H), 3.60-3.95 (m, 12H), 2.62-3.15 (m, 15H), 1.45-1.84 (m, 3H), 1.29 (m, 4H), 0.89 (d, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.9; MS (ESI) 723 (M+Na).

#### Example 4

Mono-2,2,2-trifluoroethyl mono-lactate 8: To a solution of 7 (754mg, 1 mmol) and N, N-dicyclohexylcarbodiimide (1.237 g, 6 mmol) in pyridine (10 mL) was added ethyl lactate



(2.26 mL, 20 mmol). The solution was stirred for 4.5h at 70°C. The mixture was concentrated and the residue was suspended in diethyl ether (5 mL) and dichloromethane (5 mL) and filtered. The solid was washed a few times with diethyl ether. The combined filtrate was concentrated and the crude product was chromatographed on silica gel, eluting with EtOAc and hexane to provide compound 8 (610 mg, 71%) as a foam. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.71 (d, 2H), 7.16 (d, 2H); 6.99 (d, 2H), 6.88 (dd, 2H), 5.66 (d, 1H), 4.95-5.09 (m, 2H), 4.19-4.65 (m, 6H), 3.71-4.00 (m, 9H), 2.76-3.13 (m, 6H), 1.57-1.85 (m, 7H), 1.24-1.34 (m, 4H), 0.91 (dd, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 20.29, 21.58; MS (ESI) 855 (M+1).

#### 10 Example 1

Boc-protected hydroxylamine 1: A solution of diethyl hydroxymethyl phosphonate triflate (0.582 g, 1.94 mmol) in dichloromethane (19.4 mL) was treated with triethylamine (0.541 mL, 3.88 mmol). Tert-butyl N-hydroxy-carbamate (0.284 g, 2.13 mmol) was added and the reaction mixture was stirred at room temperature overnight. The mixture was partitioned between dichloromethane and water. The organic phase was washed with saturated NaCl, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (1/1 – ethyl acetate/hexane) affording the BOC-protected hydroxylamine 1 (0.41 g, 75%) as an oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.83 (s, 1H), 4.21 (d, 2H), 4.18 (q, 4H), 1.47 (s, 9H), 1.36 (t, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 19.3.

20

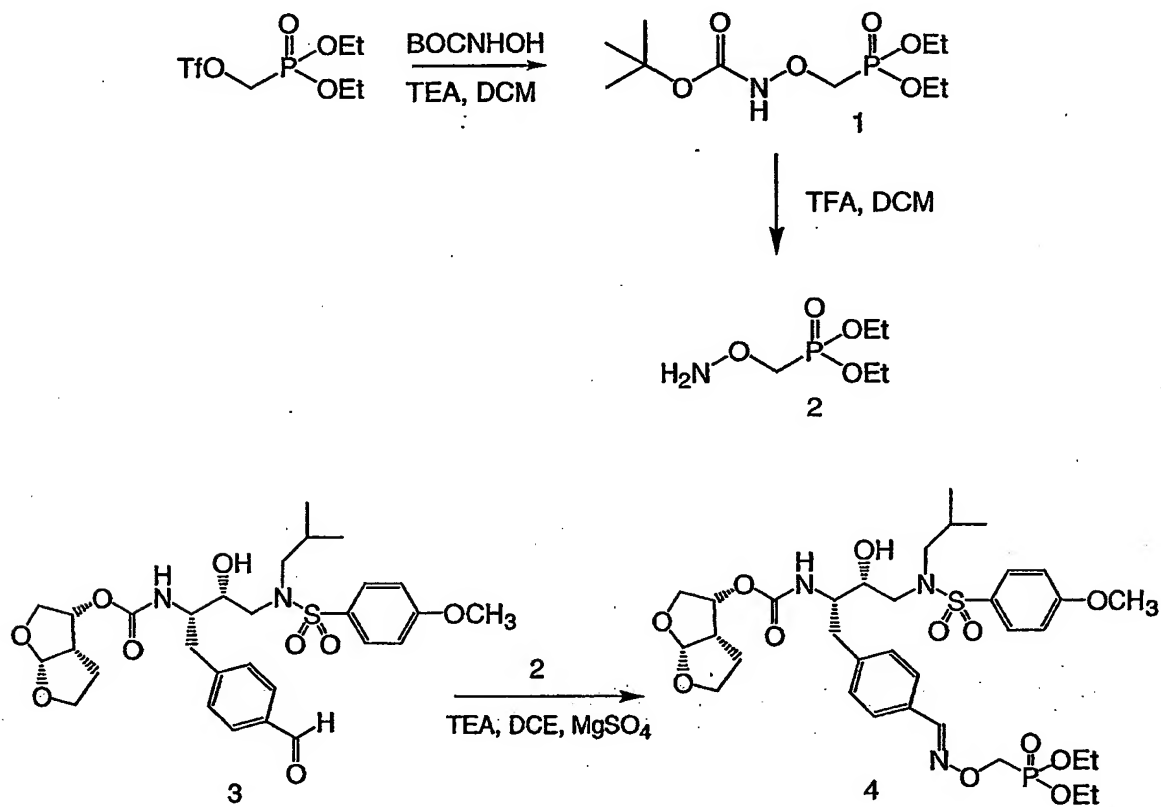
#### Example 2

Hydroxylamine 2: A solution of BOC-protected hydroxylamine 1 (0.305 g, 1.08 mmol) in dichloromethane (2.40 mL) was treated with trifluoroacetic acid (0.829 mL, 10.8 mmol). The reaction was stirred for 1.5 hours at room temperature and then the volatiles were evaporated under reduced pressure with toluene to afford the hydroxylamine 2 (0.318 g, 100%) as the TFA salt which was used directly without any further purification: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 10.87 (s, 2H), 4.45 (d, 2H), 4.24 (q, 4H), 1.38 (t, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 16.9; MS (ESI) 184 (M+H).

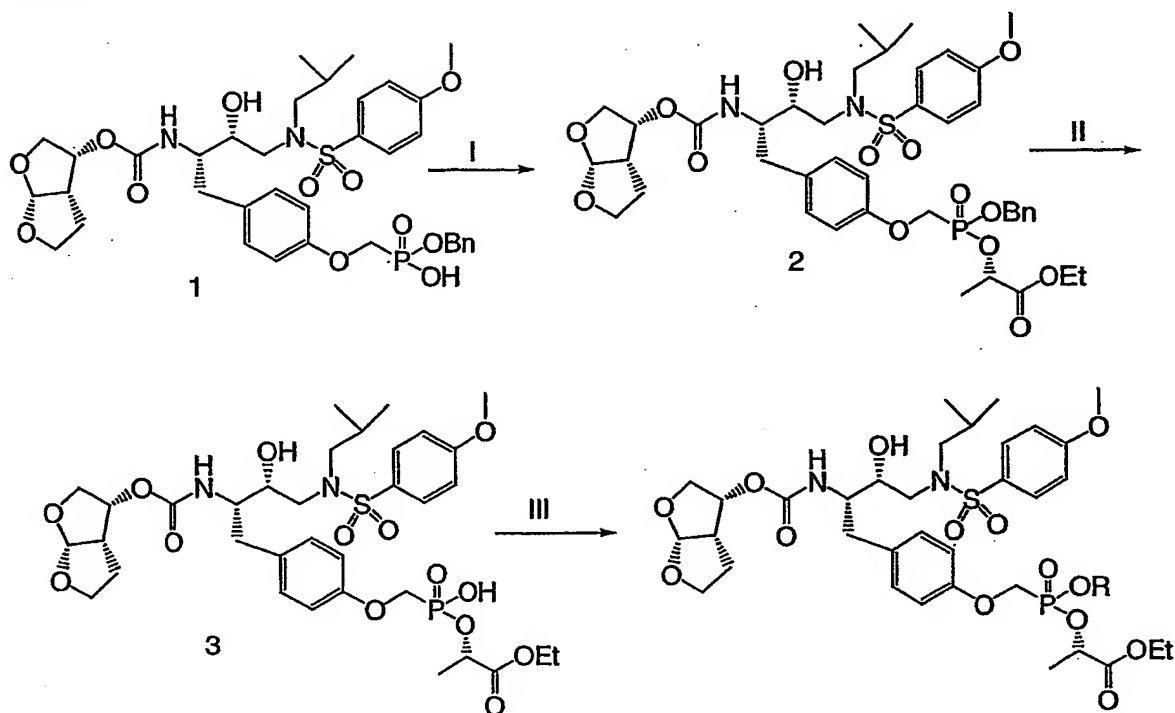
#### 30 Example 3

Oxime 4: To a solution of aldehyde 3 (96 mg, 0.163 mmol) in 1,2-dichloroethane (0.65 mL) was added hydroxylamine 2 (72.5 mg, 0.244 mmol), triethylamine (22.7 μL, 0.163 mmol) and MgSO<sub>4</sub> (10 mg). The reaction mixture was stirred at room temperature for 2 hours then

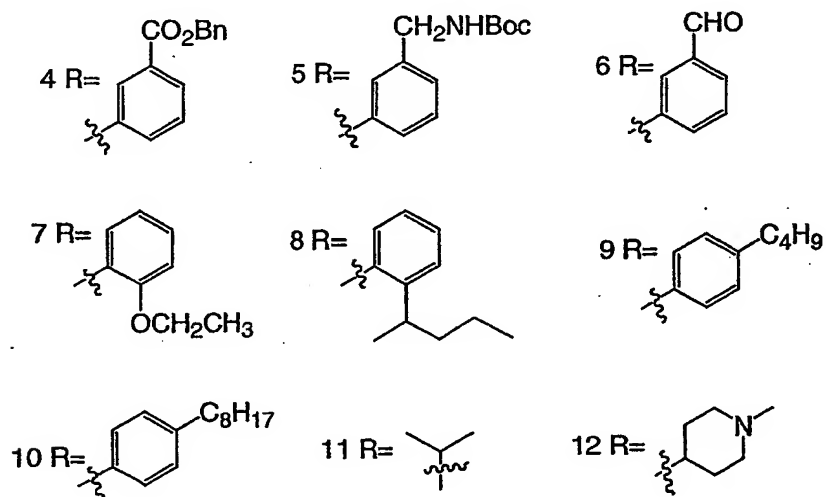
the mixture was partitioned between dichloromethane and water. The organic phase was washed with saturated NaCl, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (90/10 – ethyl acetate/hexane) affording, GS-277771, oxime 4 (0.104 g, 85%) as a solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.13 (s, 1H), 7.72 (d, 2H), 7.51 (d, 2H), 7.27 (d, 2H), 7.00 (d, 2H), 5.67 (d, 1H), 5.02 (m, 2H), 4.54 (d, 2H), 4.21 (m, 4H), 3.92 (m, 1H), 3.89 (s, 3H), 3.88 (m, 1H), 3.97-3.71 (m, 2H), 3.85-3.70 (m, 2H), 3.16-2.99 (m, 2H), 3.16-2.81 (m, 7H), 1.84 (m, 1H), 1.64-1.48 (m, 2H), 1.37 (t, 6H), 0.94-0.90 (dd, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 20.0; MS (ESI) 756 (M+H).

10 Scheme 1

Scheme 1



I. Ethyl(S)-(-)lactate/Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate/  
 DIPEA/EtOAc; II.  $H_2$ /20%Pd-C/EtOAc-EtOH; III. ROH/Benzotriazol-1-  
 yloxytripyrrolidinophosphonium hexafluorophosphate/ DIPEA/EtOAc



Example 1

Compound 1 was prepared according to methods from previous Schemes

Example 2

- 5 Compound 2: To a solution of compound 1 (5.50 g, 7.30 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (5.70g, 10.95 mmol), and Ethyl(S)-(-)-lactate (1.30 g, 10.95 mmol) in DMF (50 mL) was added Diisopropylethylamine (5.08 mL, 29.2 mmol). The mixture was stirred for 7 hours after which was diluted in EtOAc. The organic phase was washed with H<sub>2</sub>O (5X), brine, dried over MgSO<sub>4</sub> and *concentrated in*  
10 *vacuo*. The residue was purified by silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/Isopropanol= 100/4) to give 3.45 g of compound 2.

Example 3

- Compound 3: To the mixture of compound 2 (3.45 g) in EtOH/EtOAc (300 mL/100 mL) was  
15 added 20% Pd/C (0.700 g). The mixture was hydrogenated for 1 hour. Celite was added and the mixture was stirred for 10 minutes. The mixture was filtered through a pad of celite and washed with ethanol. Concentration gave 2.61 g of compound 3.

Example 4

- 20 Compound 4: To a solution of compound 3 (1.00 g, 1.29 mmol) in dry dimethylformamide (5 mL) was added 3-Hydroxy-benzoic acid benzyl ester (0.589 g, 2.58 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (1.34 g, 2.58 mmol), followed by addition of Diisopropylethylamine (900  $\mu$ L, 5.16 mmol). The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over  
25 sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/Isopropanol= 100/3) to provide 67.3 mg of compound 4: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.91 (2H, d, J=8.9 Hz), 7.75 (2H, m), 7.73-7.3 (13H, m), 7.25 (2H, m), 7.21-6.7 (6H, m), 5.87 (1H, m), 5.4-4.8 (6H, m), 4.78-4.21 (4H, m), 3.98 (3H, s), 2.1-1.75 (8H, m), 1.55 (3H, m), 1.28 (3H, m), 0.99 (6H, m).

30

Example 5

Compound 5: To a solution of compound 3 (1.40 g, 1.81 mmol) in dry dimethylformamide (5 mL) was added (4-Hydroxy-benzyl)-carbamic acid tert-butyl ester (0.80 g, 3.62 mmol),

Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (1.74 g, 3.62 mmol), followed by addition of Diisopropylethylamine (1.17 ml, 7.24 mmol). The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography ( $\text{CH}_2\text{Cl}_2/\text{Isopropanol}=100/3.5$ ) to provide 770 mg of compound 5:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.8(2H, d,  $J=8.9\text{Hz}$ ), 7.4 (2H, m), 7.3-6.8 (8H, m), 5.75 (1H, m), 5.3-5.1(2H, m), 4.6-4.23 (4H,m), 3.98 (3H, s), 3.7-2.6 (15H, m), 2.2-1.8 (12H, m), 1.72 (3H, s), 1.58(3H, m), 1.25 (3H, m), 0.95 (6H, m).

#### 10 Example 6

Compound 6: To a solution of compound 3 (1.00 g, 1.29 mmol) in dry dimethylformamide (6 mL) was added 3-Hydroxybenzaldehyde (0.320 g, 2.60 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (1.35 g, 2.60 mmol), followed by addition of Diisopropylethylamine (901  $\mu\text{L}$ , 5.16 mmol). The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography ( $\text{CH}_2\text{Cl}_2/\text{Isopropanol}=100/5$ ) to provide 880 mg of compound 6.

#### 20 Example 7

Compound 7: To a solution of compound 3 (150 mg, 0.190 mmol) in dry dimethylformamide (1 mL) was added 2-Ethoxy-phenol (48.0  $\mu\text{L}$ , 0.380 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (198 mg, 0.380 mmol), followed by addition of Diisopropylethylamine (132  $\mu\text{L}$ , 0.760 mmol). The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography ( $\text{CH}_2\text{Cl}_2/\text{Isopropanol}=100/4$ ) to provide 84.7 mg of compound 7:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.73 (2H, d,  $J=8.9\text{ Hz}$ ), 7.15 (2H, m), 7.01-6.9 (8H, m), 5.66 (1H, m), 5.22-5.04 (2H, m), 4.56- 4.2 (6H, m), 4.08 (2H, m), 3.89 (3H, m), 3.85-3.69 (6H, m), 3.17-2.98 (7H, m), 2.80(3H, m) 1.86 (1H, m), 1.65(2H, m), , 1.62-1.22 (6H, m), 0.92(6H, m).

#### Example 8

Compound 8: To a solution of compound 3 (50.0 mg, 0.0650 mmol) in dry dimethylformamide (1 mL) was added 2-(1-methylbutyl) phenol (21.2 mg, 0.130 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (67.1 mg, 0.130 mmol), followed by addition of Diisopropylethylamine (45.0  $\mu$ L, 0.260 mmol). The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reversed phase HPLC to provide 8.20 mg of compound 8:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.73 (2H, d, J=8.9 Hz), 7.25 (2H, m), 7.21-6.89 (8H, m), 5.7(1H, m), 5.29-4.9 (2H, m), 4.56-4.2 (6H, m), 3.89 (3H, m), 3.85-3.69 (6H, m), 3.17-2.89 (8H, m), 2.85(3H, m), 2.3-1.65(4H, m), 1.55-1.35 (6H, m), 0.92(6H, m).

#### Example 9

Compound 9: To a solution of compound 3 (50.0 mg, 0.0650 mmol) in dry dimethylformamide (1 mL) was added 4-N-Butylphenol (19.4 mg, 0.130 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (67.1 mg, 0.130 mmol), followed by addition (45.0  $\mu$ L, 0.260 mmol) of Diisopropylethylamine. The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reversed phase HPLC to provide 9.61 mg of compound 9:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.8(2H, d, J=8.9 Hz), 7.4 (2H, m), 7.3-6.8 (8H, m), 5.75 (1H, m), 5.3-4.5 (4H, m), 4.3-3.4.1 (4H, m), 3.9 (3H, m), 3.3-2.59 (11H, m), 2.25 (2H, m), 1.85-1.5 (5H, m), 1.4-1.1(10H, m), 0.95(9H, m).

#### Example 10

Compound 10: To a solution of compound 3 (50.0 mg, 0.0650 mmol) in dry dimethylformamide (1 mL) was added 4-Octylphenol (26.6 mg, 0.130 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (67.1 mg, 0.130 mmol), followed by addition of Diisopropylethylamine (45.0  $\mu$ L, 0.260 mmol). The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reversed phase HPLC to provide 7.70 mg of compound 10:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.75 (2H, d, J=8.9 Hz), 7.3 (2H, m), 7.2-6.8 (8H, m), 5.70 (1H, m), 5.3-4.9 (4H, m), 4.6-3.9 (4H, m),

3.89 (3H, m), 3.85-2.59 (12H, m), 2.18-1.75 (10H, m), 1.69-1.50 (8H, m), 1.4-1.27(6H,m), 0.95(9H, m).

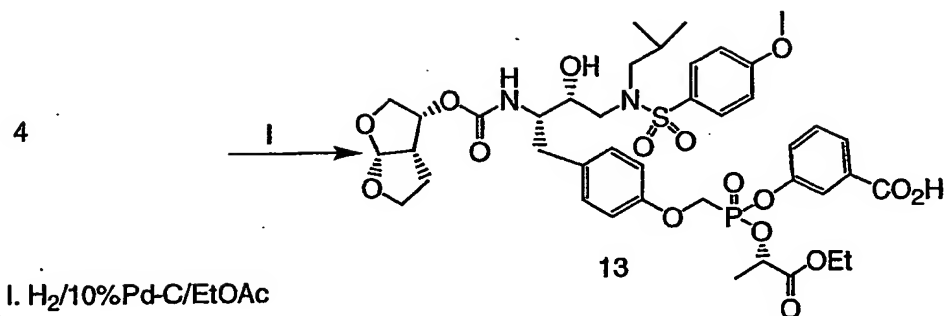
#### Example 11

5 Compound 11: To a solution of compound 3 (100 mg, 0.120 mmol) in dry dimethylformamide (1 mL) was added Isopropanol (20.0  $\mu$ L, 0.240 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (135 mg, 0.240 mmol), followed by addition of Diisopropylethylamine (83.0  $\mu$ L, 0.480 mmol). The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over  
10 sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography ( $\text{CH}_2\text{Cl}_2$ /Isopropanol= 100/4) to provide 12.2 mg of compound 11:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71 (2H, d, J=8.9 Hz), 7.15 (2H, m), 7.0 (2H, m), 6.89 (2H, m), 5.65 (1H, m), 5.03-4.86(4H, m), 4.34-4.19 (3H, m), 3.89 (3H, s), 3.88 (1H, m), 3.82 (2H, m), 3.65 (4H, m), 3.2-2.9 (11H, m), 2.80(3H, m) 1.65(2H, m), 1.86 (1H, m), 1.6(3H, m),  
15 1.30(3H,m), 0.92(6H, m).

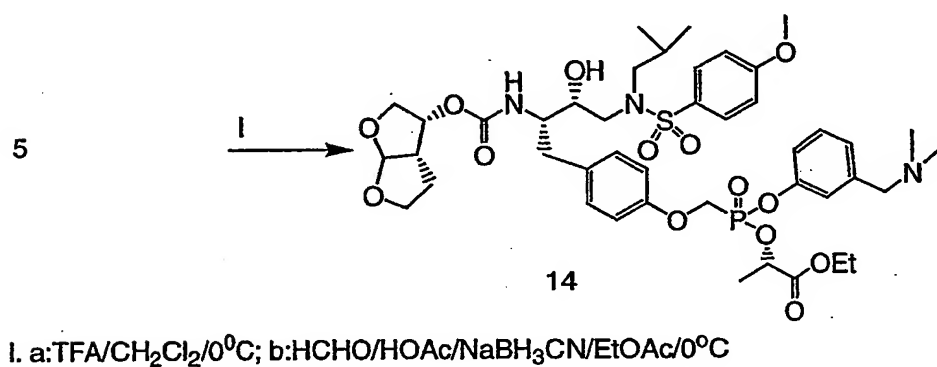
#### Example 12

Compound 12: To a solution of compound 3 (100 mg, 0.120 mmol) in dry dimethylformamide (1mL) was added 4-Hydroxy-1-methylpiperidine (30.0 mg, 0.240  
20 mmol), Benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (135 mg, 0.240 mmol), followed by addition of Diisopropylethylamine (83.0  $\mu$ L, 0.480 mmol). The mixture was stirred for 14 hours, the resulting residue was diluted in EtOAc, washed with brine (3x) and dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reversed phase HPLC to provide 50.1 mg of compound 12:  $^1\text{H}$  NMR  
25 ( $\text{CDCl}_3$ )  $\delta$  7.73 (2H, d, J=8.9 Hz), 7.18 (2H, m), 7.0 (2H, m), 6.9 (2H, m), 5.67 (1H, m), 5.2-4.9 (4H, m), 4.30-4.11 (4H, m), 3.98 (1H, m), 3.89 (3H, s), 3.87 (1H, m), 3.75 (2H, m), 3.5-3.3 (4H, m), 3.2-2.9 (14H, m), 2.80(3H, m) 1.65(2H, m), 1.86 (1H, m), 1.6(3H, m), 1.30(3H,m), 0.92(6H, m).

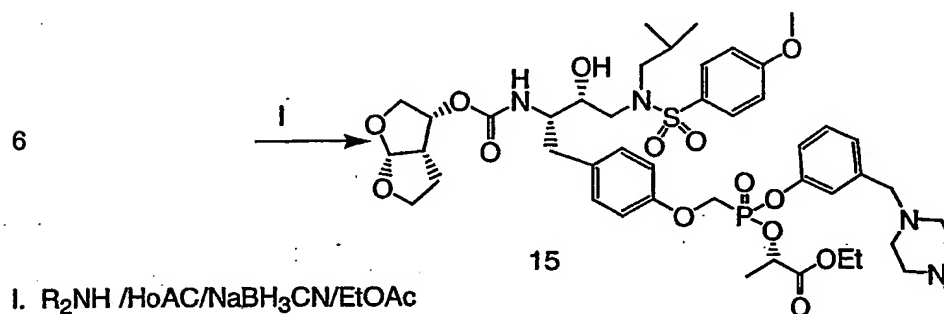
## Scheme 2



## Scheme 3



## Scheme 4



5

## Example 13

Compound 13: To a solution of compound 4 (4.9 g) in EtOAc (150ml) was added 20% Pd/C (0.90 g), the reaction mixture was hydrogenated for 1 hour. Celite was added and the mixture was stirred for 10 minutes. The mixture was filtered through a pad of celite and washed with ethanol. Concentration gave 4.1 g of compound 13:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.91 (2H, d,  $J=8.9$  Hz),



7.75 (2H, m), 7.73-7.3 (8H, m), 7.25 (2H, m), 7.21-6.7(6H, m), 5.4-4.8(6H, m), 4.78-4.21 (4H, m), 3.98 (3H,s), 2.1-1.75 (8H, m), 1.55 (3H, m), 1.28(3H, m), 0.99(6H, m).

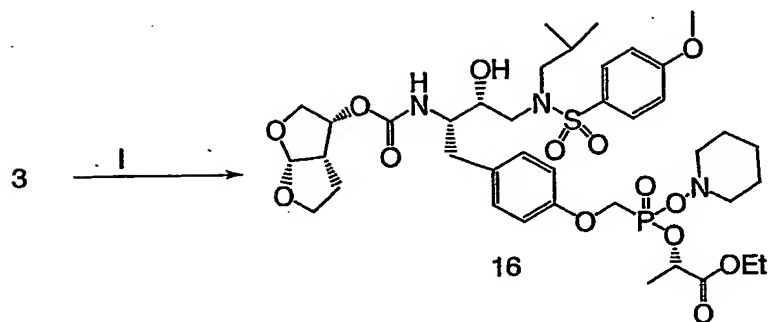
#### Example 14

- 5 Compound 14: To a solution of compound 5 (0.770 g, 0.790 mmol) in dichloromethane (10 mL), under ice-cooling, was added trifluoroacetic acid (5 mL), the resulting mixture was stirred at 25°C for two hours. The reaction mixture was concentrated under reduced pressure and the residue was co-evaporated with EtOAc to provide an yellow oil. To a solution of the above oil in (10 mL) of EtOAc, under ice-cooling and stirring was added formaldehyde (210  
10  $\mu$ L, 2.86 mmol), acetic acid (252  $\mu$ L, 4.30 mmol), followed by sodium cyanoborohydride (178 mg, 2.86 mmol). The mixture was further stirred at 25°C for 2 hours. The above mixture was concentrated and diluted with EtOAc and washed with H<sub>2</sub>O (3X), brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified using reversed-phase HPLC to provide 420 mg of compound 14: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  
15  $\delta$  7.8(2H, d, J=8.9Hz), 7.4 (2H, m), 7.3-6.8 (8H, m), 5.75 (1H, m), 5.3-5.1(2H, m), 4.6-4.23 (4H,m), 3.98 (3H, s), 3.7-2.6 (15H, m), 2.2-1.8 (8H, m), 1.72 (3H, s), 1.58(3H, m), 1.25 (3H, m), 0.95 (6H, m).

#### Example 15

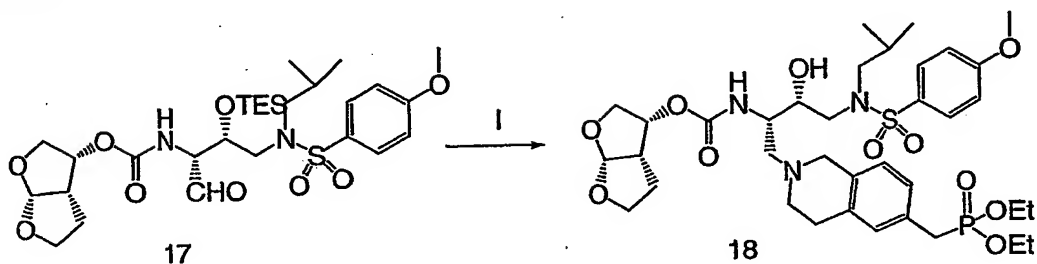
- 20 Compound 15: To a solution of compound 6 (100mg, 0.114 mmol) in EtOAc (1 mL) was added 1-Methyl-piperazine (63.2 mg, 0.570 mmol), acetic acid (34.0  $\mu$ L, 0.570 mmol) followed by Sodium Cyanoborohydride (14.3 mg, 0.228mmol). The mixture was stirred at 25°C for 14 hours. The reaction mixture was concentrated and diluted with EtOAc and washed with H<sub>2</sub>O (5X), brine (2x), dried over sodium sulfate, filtered, and concentrated under reduced pressure.  
25 The residue was purified using silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/Isopropanol= 100/6.5) to give 5.22 mg of compound 15: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.73 (2H, d, J=8.9 Hz), 7.4-7.18(8H, m), 7.1-6.89 (2H, m), 5.67 (1H, m), 5.2-4.9 (4H, m), 4.30-4.11 (4H, m), 3.98 (1H, m), 3.89 (3H, s), 3.87 (1H, m), 3.75 (2H, m), 3.5-3.3 (4H, m), 3.2-2.9 (10H, m), 2.80-2.25 (8H,m) 1.65(2H, m), 1.86 (1H, m), 1.6(3H, m), 1.30(3H,m), 0.92(6H, m).

## Scheme 5



I. Piperidin-1-ol/DCC/Pyridine

## Scheme 6

I. a: R<sub>2</sub>NH /HOAc/NaBH<sub>3</sub>CN/EtOAc b: 2% HF/CH<sub>3</sub>CN

## Example 16

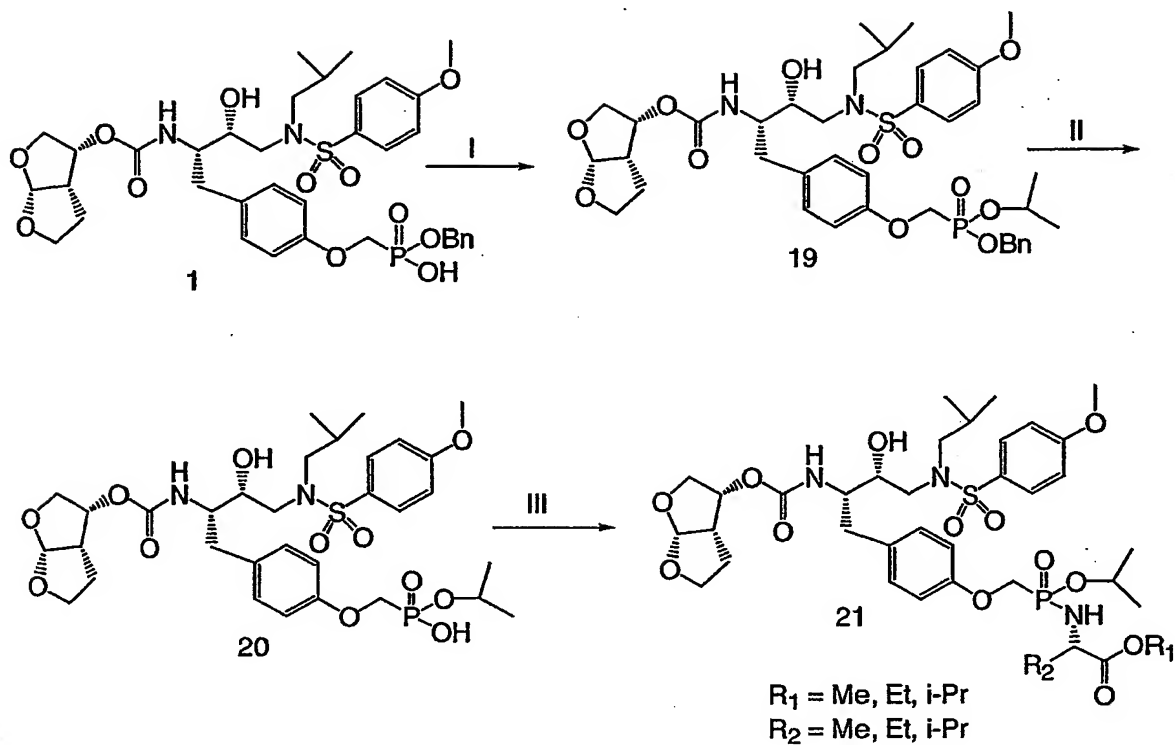
Compound 16: To a solution of compound 3 (100mg, 0.120 mmol) in Pyridine (600  $\mu$ L) was  
 5 added Piperidin-1-ol (48.5 mg, 0.480 mmol), followed by N,N-Dicyclohexylcarbodiimide  
 (99.0 mg, 0.480 mmol). The mixture was stirred for 6 hours, the solvent was concentrated  
 under reduced pressure. The resulting residue was purified by silica gel chromatography  
 (CH<sub>2</sub>Cl<sub>2</sub>/Methanol= 100/5) to provide 17 mg of compound 16: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.73 (2H,  
 d, J=8.9 Hz), 7.16 (2H, m), 7.0 (2H, m), 6.9 (2H, m), 5.68 (1H, m), 5.17 (1H, m), 5.04 (1H,  
 10 m), 4.5-4.2 (4H, m), 3.90 (3H, s), 3.75 (2H, m), 3.5-3.3 (4H, m), 3.2-2.9 (10H, m), 2.80 (3H,  
 m) 1.65 (2H, m), 1.86 (1H, m), 1.6 (3H, m), 1.5-1.27 (9H, m), 0.92 (6H, m).

Example 17

Compound 18: To a solution of compound 17 (148 mg, 0.240 mmol) in 4 mL of Methanol was added (1,2,3,4-Tetrahydro-isoquinolin-6-ylmethyl)-phosphonic acid diethyl ester (70.0 mg, 0.240 mmol), acetic acid (43.0  $\mu$ L, 0.720 mmol). The reaction mixture was stirred for 3 minutes, followed by addition of Sodium Cyanoborohydride (75.3 mg, 1.20 mmol). The reaction mixture was stirred at 25°C for 14 hours. The reaction mixture was diluted with EtOAc and washed with H<sub>2</sub>O (3X), brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified using silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/Isopropanol= 100/5) to give 59 mg of TES-protected intermediate.

83  $\mu$ L of 48% HF solution was added to acetonitrile (4 mL) to prepare the 2% HF solution. The above 2% HF solution was added to TES protected intermediate (47 mg, 0.053 mmol) and the reaction mixture was stirred for 2 hours. The solvent was concentrated and the residue was diluted with EtOAc, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified using silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/Methanol= 100/10) to give 35.2 mg of compound 18: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.73 (2H, d, J=8.9 Hz), 7.05 (2H, m), 6.89 (2H, m), 6.76 (1H, m), 5.75 (1H, m), 5.67 (1H, m), 5.3 (2H, m), 4.2-3.6 (12 H, m), 3.4-2.4 (11 H, m), 2.1-1.8 (6H, m), 1.4-1.28 ( 8 H, m), 0.92(6H, m).

Scheme 7

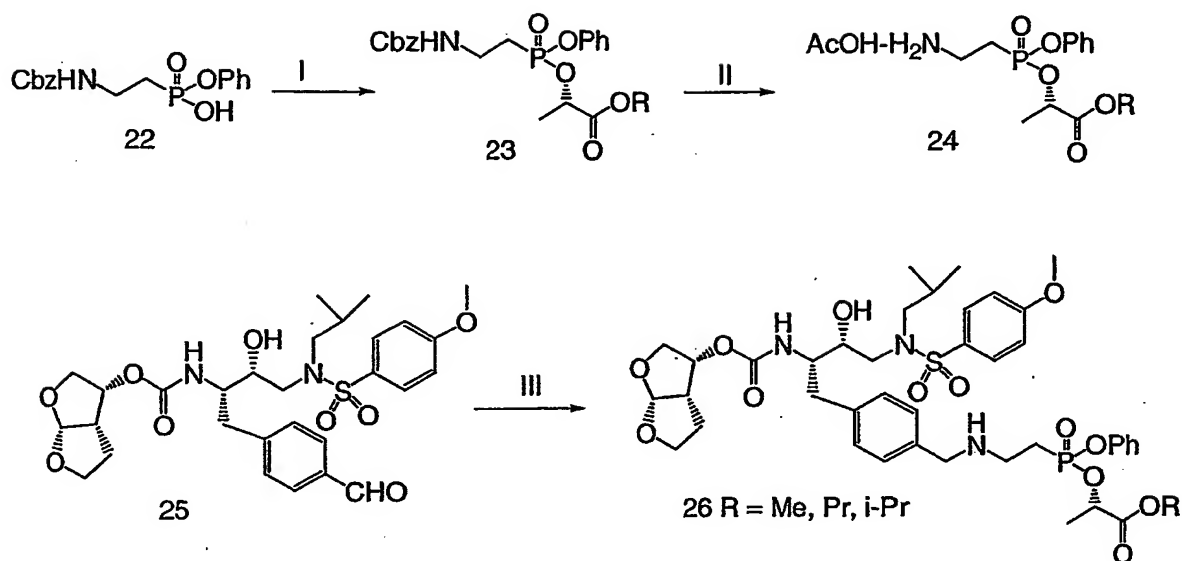


I. Isopropanol/Benzotriazol-1-yloxytripyrrolidinophosphonium  
 hexafluorophosphate/ DIPEA/DMF;  
 II.  $\text{H}_2$ /10%Pd-C/EtOAc-EtOH;  
 III.  $\text{RNH}_2$ /Aldrithiol-2/ $\text{PPh}_3$ / $\text{iPr}_2\text{NEt}$ /pyridine

Compound 19 is prepared following the procedure for compound 2 by using monoacid 1.

- 5 Compound 20 is made following a hydrogenation of compound 19. Mono acid 20 reacts with corresponding amino esters in the presence of Aldrithiol-2 and triphenylphosphine to form compound 21.

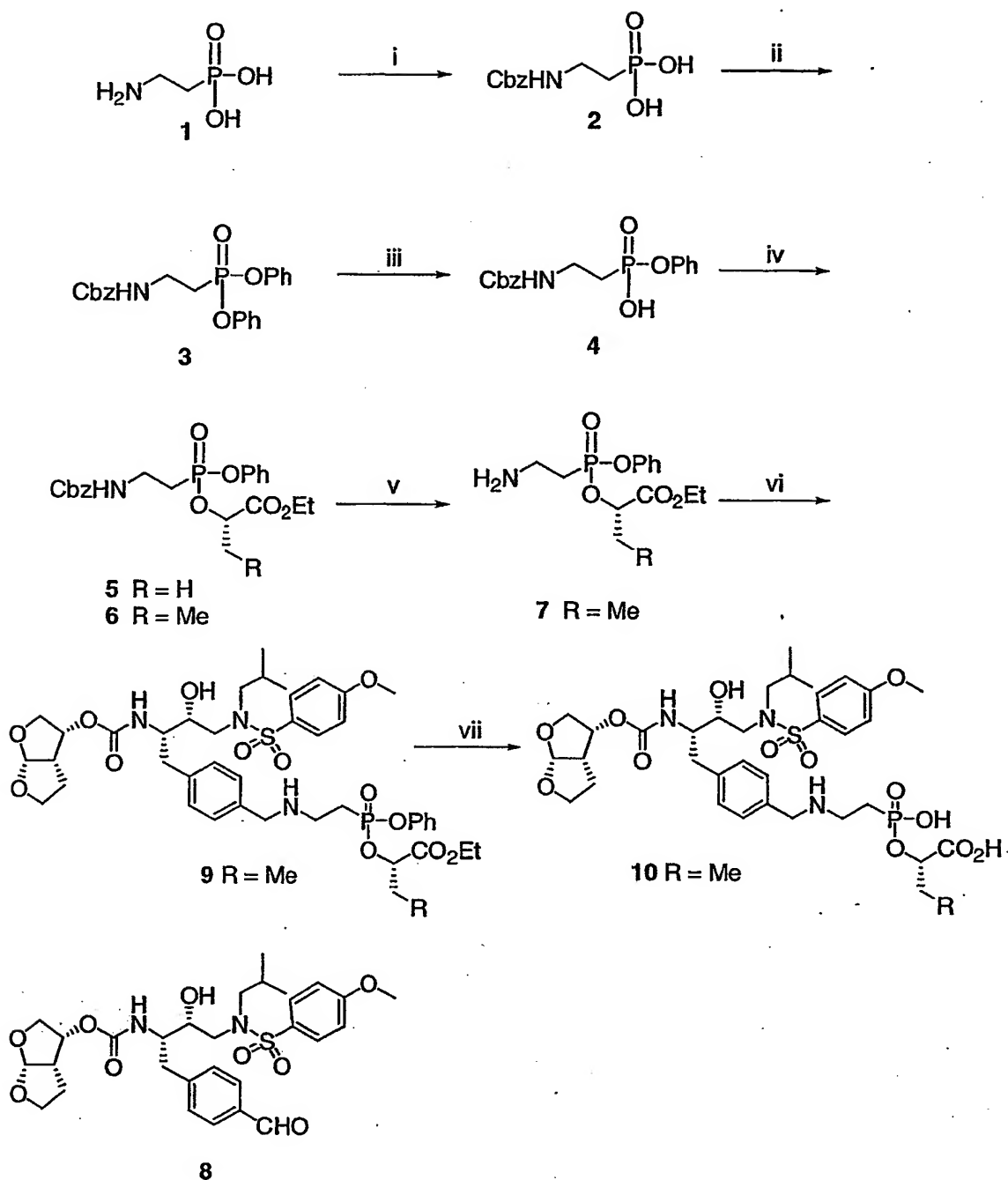
## Scheme 8



I. a. SOCl<sub>2</sub>/60 °C; b. Alkyl (s)-lactate/Et<sub>3</sub>N; II. H<sub>2</sub>/10%Pd-C/EtOAc-HOAc;  
 III. a. compound 25/MgSO<sub>4</sub>; b. HOAc/NaBH<sub>3</sub>CN

- Monoacid 22 is treated with thionyl chloride at 60°C to form monochloridate, which reacts with corresponding alkyl (s)-lactate to generate monolactate 23. Monolactate 23 is
- 5 hydrogenated with 10%Pd-C in the presence of acetic acid to form amine 24. Aldehyde 25 reacts with amine 24 in the presence of MgSO<sub>4</sub> to form the intermediate imine, which is reduced with sodium cyanoborohydride to afford compound 26.

Scheme 1



**Reagents and conditions:** i. CbzCl, NaOH, tol/H<sub>2</sub>O, 100%; ii. a. SOCl<sub>2</sub>, DMF, tol, 65°C; b. PhOH, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 71%; iii. aq. NaOH, CH<sub>3</sub>CN, 79%; iv. a. SOCl<sub>2</sub>, DMF, tol, 65°C; b. ethyl lactate, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, (5) 85%; 2-hydroxy butyric acid ethyl ester, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, (6) 75%; v. H<sub>2</sub>, AcOH, 10% Pd/C, EtOH, 94%; vi. a. 7 + 8, 1,2-DCE, MgSO<sub>4</sub>; b. NaBH<sub>3</sub>CN, AcOH, 50%; vii. pig liver esterase, 20% DMSO/PBS, 40°C, 25%.

Example 1

Compound 2: A 3L, 3-neck flask was equipped with a mechanical stirrer and addition funnel and charged with 2-aminoethyl phosphonic acid (60.0g, 480 mmol). 2N Sodium hydroxide (480 mL, 960 mmol) was added and flask cooled to 0°C. Benzyl chloroformate (102.4 g, 600 mmol) in toluene (160mL) was added dropwise with vigorous stirring. The reaction mixture was stirred at 0°C for 30 minutes, then at room temperature for 4 h. 2N sodium hydroxide (240 mL, 480 mmol) was added, followed by benzyl chloroformate (20.5 g, 120 mmol) and the reaction mixture was vigorously stirred for 12 h. The reaction mixture was washed with diethyl ether (3x). The aqueous layer was acidified to pH 2 with concentrated HCl to give a white precipitate. Ethyl acetate was added to the mixture and concentrated HCl (80 mL, 960 mmol) was added. The aqueous layer was extracted with ethyl acetate and combined organic layer was dried (MgSO<sub>4</sub>) and concentrated to give a waxy, white solid (124 g, 479 mmol, 100%). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.45-7.30 (m, 5 H, Ar), 5.06 (d, *J* = 14.7 Hz, 2 H, CH<sub>2</sub>Ph), 3.44-3.31 (m, 2 H, NCH<sub>2</sub>CH<sub>2</sub>), 2.03-1.91 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>P); <sup>31</sup>P NMR (121 MHz, CD<sub>3</sub>OD): δ 26.3.

Example 2

Compound 3: To a mixture of compound 2 (50.0 g, 193 mmol) in toluene (1.0 L) was added DMF (1.0 mL) followed by thionyl chloride (56 mL, 768 mmol). The reaction mixture was heated at 65°C for 3-4 h under a stream of argon. The reaction mixture was cooled to room temperature and concentrated. Residual solvent was removed under high vacuum for 1 h. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1.0 L) and cooled to 0°C. Triethylamine (161 mL, 1158 mmol) was added, followed by phenol (54.5 g, 579 mmol). The reaction mixture was warmed to room temperature overnight, then washed with 1.0N HCl, saturated NaHCO<sub>3</sub> solution, brine and dried (MgSO<sub>4</sub>). Concentrated and purified (silica gel, 1:1 EtOAc/Hex) to give a pale yellow solid (56 g, 136 mmol, 71%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.40-7.10 (m, 15 H, Ar), 5.53 (br s, 1 H, NH), 5.11 (br s, 2 H, CH<sub>2</sub>Ph), 3.72-3.60 (m, 2 H, NCH<sub>2</sub>CH<sub>2</sub>), 2.49-2.30 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>P); <sup>31</sup>P NMR (121 MHz, CDCl<sub>3</sub>): δ 22.9.

Example 3

Compound 4: To a solution of compound 3 (64 g, 155.6 mmol) in acetonitrile (500 mL) at 0°C was added 2.0M sodium hydroxide. The reaction mixture was stirred at 0°C for 30 min, then at room temperature for 2.5 h. The reaction mixture was concentrated to 100 mL and diluted with H<sub>2</sub>O (500 mL). The aqueous solution was washed with EtOAc (3 x 300 mL).  
5 The aqueous layer was acidified to pH 1 with concentrated HCl, producing a white precipitated. The mixture was extracted with EtOAc (4 x 300 mL) and combined organic layer was washed with brine and dried (MgSO<sub>4</sub>). Concentration gave a solid, which was recrystallized from hot EtOAc (450 mL) to give a white solid (41.04 g, 122 mmol, 79%). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.45-7.10 (m, 10 H, Ar), 5.09 (s, 2 H, CH<sub>2</sub>Ph), 3.53-3.30 (m, 2 H, NCH<sub>2</sub>CH<sub>2</sub>), 2.25-2.10 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>P); <sup>31</sup>P NMR (121 MHz, CD<sub>3</sub>OD): δ 24.5.  
10

#### Example 4

Compound 5: To a mixture of compound 4 (28 g, 83 mmol) in toluene (500 mL) was added DMF (1.0 mL), followed by thionyl chloride (36.4 mL, 499 mmol). The mixture was heated  
15 at 65°C for 2 h providing a pale yellow solution. The reaction mixture was concentrated and dried for 45 min under high vacuum. The residue was dissolved in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (350 mL) and cooled to 0°C. Triethylamine (45.3 mL, 332 mmol) was added slowly, followed by the dropwise addition of ethyl lactate (18.8 mL, 166 mmol). The reaction mixture was stirred at 0°C for 30 min, then warmed to room temperature overnight. The reaction mixture was  
20 diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with 1 N HCl, saturated NaHCO<sub>3</sub> solution, brine and dried (MgSO<sub>4</sub>). Concentration and purification (silica gel, 1:5 to 1:0 EtOAc/Hex) gave a pale yellow oil (30.7 g, 71 mmol, 85%) as a mixture of diastereomers which were separated by HPLC (Dynamax reverse phase C-18 column, 60% acetonitrile/H<sub>2</sub>O). More polar diastereomer: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.40-7.10 (m, 10 H, Ar), 5.65 (s, 1 H, NH),  
25 5.12 (s, 2 H, CH<sub>2</sub>Ph), 5.10-5.00 (m, 1 H, OCHC) 4.17 (q, J = 6.9 Hz, 2 H, OCH<sub>2</sub>CH<sub>3</sub>), 3.62 (dt, J<sub>1</sub> = 20.4 Hz, J<sub>2</sub> = 6.0 Hz, 2 H, NCH<sub>2</sub>CH<sub>2</sub>), 2.25 (dt, J<sub>1</sub> = 18.0 Hz, J<sub>2</sub> = 6.0 Hz, 2 H, CH<sub>2</sub>CH<sub>2</sub>P), 1.60 (dd, J<sub>1</sub> = J<sub>2</sub> = 6.9 Hz, 3 H, CHCH<sub>3</sub>), 1.23 (t, J = 6.9 Hz, 3 H, OCH<sub>2</sub>CH<sub>3</sub>); <sup>31</sup>P NMR (121 MHz, CDCl<sub>3</sub>): δ 26.2. Less polar diastereomer: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ  
30 7.40-7.10 (m, 10 H, Ar), 5.87 (s, 1 H, NH), 5.13 (s, 2 H, CH<sub>2</sub>Ph), 5.10-5.00 (dq, J<sub>1</sub> = J<sub>2</sub> = 6.9 Hz, 1 H, OCHC) 4.22 (q, J = 7.2 Hz, 2 H, OCH<sub>2</sub>CH<sub>3</sub>), 3.68 (dt, J<sub>1</sub> = 21.6 Hz, J<sub>2</sub> = 6.9 Hz, 2 H, NCH<sub>2</sub>CH<sub>2</sub>), 2.40-2.20 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>P), 1.49 (dd, J<sub>1</sub> = 70.2 Hz, J<sub>2</sub> = 6.9 Hz, 3 H, CHCH<sub>3</sub>), 1.28 (t, J = 6.9 Hz, 3 H, OCH<sub>2</sub>CH<sub>3</sub>); <sup>31</sup>P NMR (121 MHz, CDCl<sub>3</sub>): δ 28.3.



Example 5

Compound 6: 2-Hydroxy-butyric acid ethyl ester was prepared as follows: To a solution of L-2-aminobutyric acid (100g, 970 mmol) in 1.0 N H<sub>2</sub>SO<sub>4</sub> (2 L) at 0°C was added NaNO<sub>2</sub> (111 g, 1610 mmol) in H<sub>2</sub>O (400 mL) over 2 h. The reaction mixture was stirred at room temperature for 18h. Reaction mixture was extracted with EtOAc (4x) and combined organic layer was dried (MgSO<sub>4</sub>) and concentrated to give a yellow solid (41.5 g). This solid was dissolved in absolute ethanol (500 mL) and concentrated HCl (3.27 mL, 39.9 mmol) was added. Reaction mixture was heated to 80°C. After 24 h, concentrated HCl (3 mL) was added and reaction continued for 24 h. Reaction mixture was concentrated and product was distilled to give a colorless oil (31 g, 235 mmol, 59%).

To a mixture of compound 4 (0.22 g, 0.63 mmol) in anhydrous acetonitrile (3.0 mL) was added thionyl chloride (0.184 mL, 2.52 mmol). The mixture was heated at 65°C for 1.5 h providing a pale yellow solution. The reaction mixture was concentrated and dried for 45 min under high vacuum. The residue was dissolved in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (3.3 mL) and cooled to 0°C. Triethylamine (0.26 mL, 1.89 mmol) was added slowly, followed by the dropwise addition of 2-hydroxy-butyric acid ethyl ester (0.167 mL, 1.26 mmol). The reaction mixture was stirred at 0°C for 5 min, then warmed to room temperature overnight. The reaction mixture was concentrated, dissolved in EtOAc and washed with 1.0 N HCl, saturated NaHCO<sub>3</sub> solution, brine and dried (MgSO<sub>4</sub>). Concentration and purification (silica gel, 3:2 EtOAc/Hex) gave a pale yellow oil (0.21 g, 0.47 mmol, 75%). For major diastereomer, <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.35-7.10 (m, 10 H, Ar), 5.91 (s, 1 H, NH), 5.12 (s, 2 H, CH<sub>2</sub>Ph), 4.94-4.83 (m, 1 H, OCHC), 4.27-4.12 (m, 2 H, OCH<sub>2</sub>CH<sub>3</sub>), 3.80-3.50 (m, 2 H, NCH<sub>2</sub>CH<sub>2</sub>), 2.39-2.19 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>P), 1.82-1.71 (m, 2 H, CHCH<sub>2</sub>CH<sub>3</sub>), 1.30-1.195 (m, 3 H, OCH<sub>2</sub>CH<sub>3</sub>), 0.81 (t, *J* = 7.5 Hz, 3 H, CHCH<sub>2</sub>CH<sub>3</sub>); <sup>31</sup>P NMR (120 MHz, CDCl<sub>3</sub>): δ 28.3. For minor diastereomer, <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.35-7.10 (m, 10 H, Ar), 5.74 (s, 1 H, NH), 5.11 (s, 2 H, CH<sub>2</sub>Ph), 4.98-4.94 (m, 1 H, OCHC), 4.27-4.12 (m, 2 H, OCH<sub>2</sub>CH<sub>3</sub>), 3.80-3.50 (m, 2 H, NCH<sub>2</sub>CH<sub>2</sub>), 2.39-2.19 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>P), 1.98-1.82 (m, 2 H, CHCH<sub>2</sub>CH<sub>3</sub>), 1.30-1.195 (m, 3 H, OCH<sub>2</sub>CH<sub>3</sub>), 1.00 (t, *J* = 7.5 Hz, 3 H, CHCH<sub>2</sub>CH<sub>3</sub>); <sup>31</sup>P NMR (121 MHz, CDCl<sub>3</sub>): δ 26.2.

Example 6

Compound 7: A mixture of compound 6, (0.53 g, 1.18 mmol) acetic acid (0.135 mL, 2.36 mmol) and 10% palladium on activated carbon (0.08 g) in absolute ethanol (12 mL) was stirred under a hydrogen atmosphere (1 atm) for 3 h. Reaction mixture was filtered through Celite, concentrated, and resubjected to identical reaction conditions. After 2 h, Celite was added to the reaction mixture and mixture was stirred for 2 min, then filtered through a pad of Celite and concentrated. Dried under high vacuum to give the diastomeric acetate salt as a oil (0.42 g, 1.11 mmol, 94%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.40-7.10 (m, 5 H, Ar), 5.00-4.80 (m, 1 H, OCHC), 4.28-4.10 (m, 2 H, OCH<sub>2</sub>CH<sub>2</sub>), 3.32-3.14 (m, 2 H, NCH<sub>2</sub>CH<sub>2</sub>), 2.45-2.22 (m, 2 H, CH<sub>2</sub>CH<sub>2</sub>P), 1.97 (s, 3 H, Ac), 1.97-1.70 (m, 2 H, CHCH<sub>2</sub>CH<sub>3</sub>), 1.30-1.18 (m, 3 H, OCH<sub>2</sub>CH<sub>3</sub>), 1.00 (t, *J* = 7.5 Hz, 1 H, CHCH<sub>2</sub>CH<sub>3</sub>), 0.80 (t, *J* = 7.5 Hz, 2 H, CHCH<sub>2</sub>CH<sub>3</sub>); <sup>31</sup>P NMR (121 MHz, CDCl<sub>3</sub>): δ 27.6 (major, 1.85), 26.0 (minor, 1.01).

#### Example 7

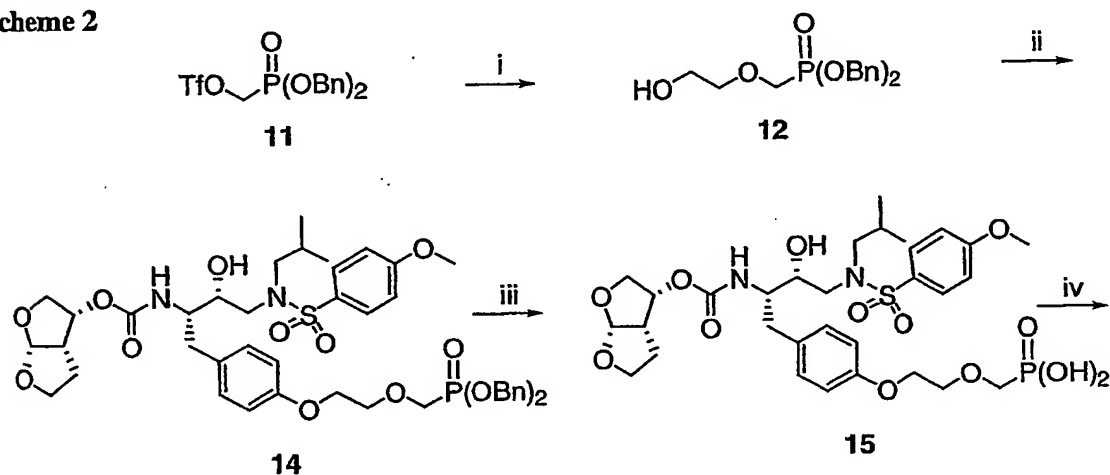
Compound 9: A solution of aldehyde 8 (0.596 g, 1.01 mmol) and compound 7 (0.42 g, 1.11 mmol) were stirred together in 1,2-dichloroethane (4.0 mL) in the presence of MgSO<sub>4</sub> for 3 h. Acetic acid (0.231 mL, 4.04 mmol) and sodium cyanoborohydride (0.127 g, 2.02 mmol) were added and reaction mixture was stirred for 50 min at room temperature. Reaction mixture was quenched with saturated NaHCO<sub>3</sub> solution, diluted with EtOAc, and vigorously stirred for 5 min. Brine was added and extracted with EtOAc (2x). Combined organic layer was dried (MgSO<sub>4</sub>) concentrated and purified (silica gel, EtOAc, then 10% EtOH/EtOAc) to give a colorless foam. Acetonitrile (4 mL) and trifluoroacetic acid (0.06 mL) were added and concentrated to a volume of 1 mL. H<sub>2</sub>O (10 mL) was added and lyophilized to give the TFA salt as a white powder (0.51 g, 0.508 mmol, 50%). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>CN): δ 7.79 (d, *J* = 8.4 Hz, 2 H, (SO<sub>2</sub>C(CH<sub>2</sub>)), 7.43-7.20 (m, 9 H, Ar), 7.10 (d, *J* = 8.4 Hz, 2 H, (CH<sub>2</sub>)COCH<sub>3</sub>), 5.85 (d, *J* = 8.4 Hz, 1 H, NH), 5.55 (d, *J* = 4.5 Hz, 1 H, OCHO), 5.00-4.75 (m, 2 H, CH<sub>2</sub>CHOC(O), POCHC), 4.39-4.05 (m, 2 H, PhCH<sub>2</sub>N, OCH<sub>2</sub>CH<sub>3</sub>), 3.89 (s, 3 H, OCH<sub>3</sub>), 3.88-3.30 (m, 9H), 3.15-2.84 (m, 5 H), 2.65-2.42 (m, 3 H), 2.10-1.68 (m, 5 H), 1.65-1.15 (m, 5 H), 1.05-0.79 (m, 9 H); <sup>31</sup>P NMR (121 MHz, CD<sub>3</sub>CN): δ 24.8 (major, 1.85), 23.1 (minor, 1.01).

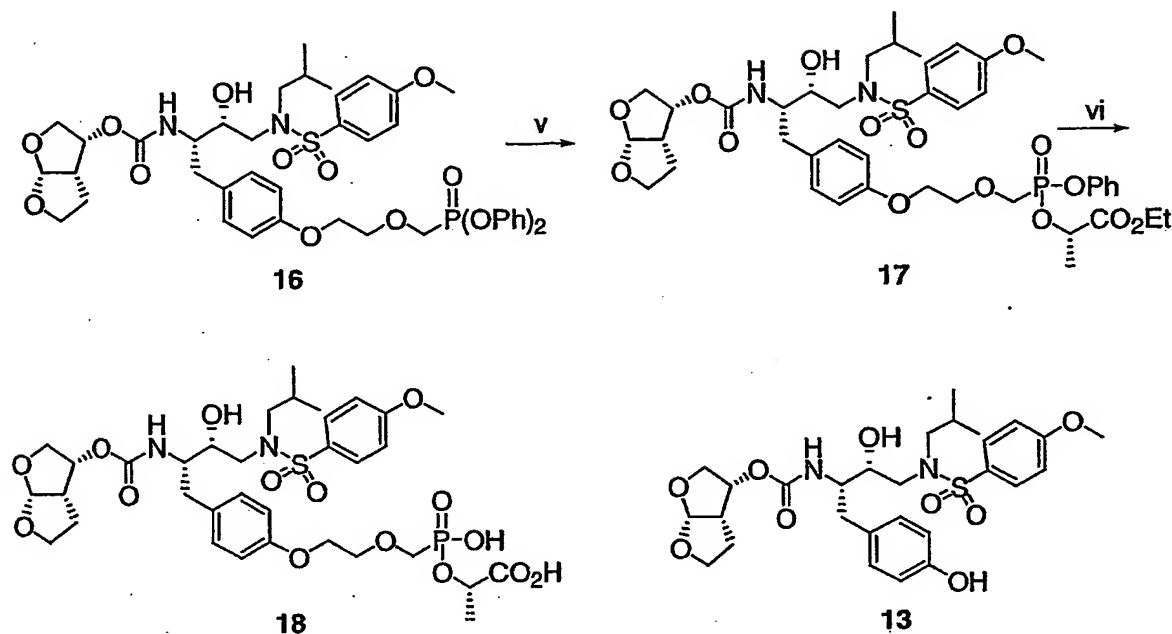
#### Example 8

Compound 10: Compound 9 (0.041 g, 0.041 mmol) was dissolved in DMSO (1.9 mL) and to this solution was added phosphate buffered saline, pH 7.4 (10 mL) and pig liver esterase

(Sigma, 0.2 mL). Reaction mixture was stirred for 24 h at 40°C. After 24 h, additional esterase (0.2 mL) was added and reaction was continued for 24 h. Reaction mixture was concentrated, resuspended in methanol and filtered. Filtrate was concentrated and purified by reverse phase chromatography to give a white powder after lyophilization (8 mg, 0.010 mmol, 25%). <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD): δ 7.78 (d, *J* = 8.9 Hz, 2 H, (SO<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>), 7.43-7.35 (m, 4 H, Ar), 7.11 (d, *J* = 8.9 Hz, 2 H, (CH<sub>2</sub>)<sub>2</sub>COCH<sub>3</sub>), 5.62 (d, *J* = 5.2 Hz, 1 H, OCHO), 4.96-4.77 (m, 2 H, CH<sub>2</sub>CHOC(O), POCHC), 4.21 (br s, 2 H, PhCH<sub>2</sub>N), 3.97-3.70 (m, 6 H), 3.90 (s, 3 H, OCH<sub>3</sub>), 3.50-3.30 (m, 3 H), 3.26-3.02 (m, 2 H), 2.94-2.58 (m, 4 H), 2.09-1.78 (m, 5 H), 1.63-1.52 (m, 2 H), 1.05-0.97 (m, 3 H); 0.94 (d, *J* = 6.7 Hz, 3 H), 0.88 (d, *J* = 6.7 Hz, 3 H); <sup>31</sup>P NMR (121 MHz, CD<sub>3</sub>OD): δ 20.8.

Scheme 2





Reagents and conditions: i. ethylene glycol,  $\text{Mg}(\text{OtBu})_2$ , DMF, 48%; ii. a.  $\text{Tf}_2\text{O}$ , 2,6-lutidine,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ ; b. **13**,  $\text{CsCO}_3$ ,  $\text{CH}_3\text{CN}$ ,  $0^\circ\text{C}$  to room temperature, 65%; iii.  $\text{H}_2$ , Pd/C, EtOH, 107%; iv. DCC, PhOH, pyr,  $70^\circ\text{C}$ , 31%; v. a. NaOH,  $\text{CH}_3\text{CN}$ ,  $0^\circ\text{C}$ ; b. DCC, ethyl lactate, pyr,  $70^\circ\text{C}$ , 52%; vi.  $\text{CH}_3\text{CN}$ , DMSO, PBS, porcine liver esterase,  $38^\circ\text{C}$ , 69%.

#### Example 9

- 5 Compound 12: To a solution of compound 11 (4.10 g, 9.66 mmol) and anhydrous ethylene glycol (5.39 mL, 96.6 mmol) in anhydrous DMF (30 mL) at  $0^\circ\text{C}$  was added powdered magnesium *tert*-butoxide (2.05 g, 12.02 mmol). The reaction mixture was stirred at  $0^\circ\text{C}$  for 1.5 h, then concentrated. The residue was partitioned between EtOAc and  $\text{H}_2\text{O}$  and washed with 1 N HCl, saturated  $\text{NaHCO}_3$  solution, and brine. Organic layer dried ( $\text{MgSO}_4$ ),
- 10 concentrated and purified (silica gel, 4% MeOH/ $\text{CH}_2\text{Cl}_2$ ) to give a colorless oil (1.55 g, 48%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.37 (s, 10 H, Ar), 5.40-5.05 (m, 4 H,  $\text{CH}_2\text{Ph}$ ), 3.84 (d,  $J = 8.1$  Hz, 2 H,  $\text{PCH}_2\text{O}$ ), 3.70-3.60 (m, 4 H,  $\text{OCH}_2\text{CH}_2\text{O}$ ,  $\text{OCH}_2\text{CH}_2\text{O}$ );  $^{31}\text{P}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  22.7.

#### 15 Example 10

Compound 14: To a solution of compound 12 (0.75 g, 2.23 mmol) and 2,6-lutidine (0.78 mL, 6.69 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 mL) at  $-78^\circ\text{C}$  was added trifluoromethanesulfonic anhydride (0.45

mL, 2.68 mmol). The reaction mixture was stirred at  $-78^{\circ}\text{C}$  for 40 min, then diluted with  $\text{CH}_2\text{Cl}_2$  and washed with 1 N HCl, saturated  $\text{NaHCO}_3$  and dried ( $\text{MgSO}_4$ ). Concentration gave a yellow oil that was dissolved in anhydrous acetonitrile (20 mL). Phenol 13 (1.00 g, 1.73 mmol) was added to the solution, which was cooled to  $0^{\circ}\text{C}$ . Cesium carbonate (0.619 g, 1.90 mmol) was added and reaction mixture was stirred at  $0^{\circ}\text{C}$  for 2 h, then at room temperature for 1.5 h. Additional cesium carbonate (0.200 g, 0.61 mmol) was added and reaction was continued for 1.5 h, then filtered. Concentration of the filtrate and purification (silica gel, 3% MeOH/ $\text{CH}_2\text{Cl}_2$ ) gave a yellow gum (1.005 g, 65%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.71 (d,  $J = 8.7$  Hz, 2 H,  $\text{SO}_2\text{C}(\text{CH})_2$ ), 7.34 (s, 10 H,  $\text{PhCH}_2\text{O}$ ), 7.11 (d,  $J = 8.1$  Hz, 2 H,  $\text{CH}_2\text{C}(\text{CH})_2(\text{CH})_2$ ), 6.98 (d,  $J = 8.7$  Hz, 2 H,  $(\text{CH})_2\text{COCH}_3$ ), 6.78 (d,  $J = 8.7$  Hz, 2 H,  $(\text{CH})_2\text{COCH}_2$ ), 5.62 (d,  $J = 5.4$  Hz, 1 H,  $\text{OCHO}$ ), 5.16-4.97 (m, 6 H), 4.05-3.65 (m, 12 H), 3.86 (s, 3 H,  $\text{OCH}_3$ ), 3.19-2.66 (m, 7 H), 1.95-1.46 (m, 3 H), 0.92 (d,  $J = 6.6$  Hz, 3 H,  $\text{CH}(\text{CH}_3)_2$ ), 0.88 (d,  $J = 6.6$  Hz, 3 H,  $\text{CH}(\text{CH}_3)_2$ );  $^{31}\text{P}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  21.9.

#### 15 Example 11

Compound 15: A mixture of compound 14 (0.410 g, 0.457 mmol) and 10% palladium on carbon (0.066 g) in ethanol (5.0 mL) was stirred under a hydrogen atmosphere (1 atm) for 16 h. Celite was added and the mixture was stirred for 5 min, then filtered through Celite and concentrated to give a foam (0.350 g, 107%).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.76 (d,  $J = 8.7$  Hz, 2 H,  $\text{SO}_2\text{C}(\text{CH})_2$ ), 7.15 (d,  $J = 8.4$  Hz, 2 H,  $\text{CH}_2\text{C}(\text{CH})_2(\text{CH})_2$ ), 7.08 (d,  $J = 8.4$  Hz, 2 H,  $(\text{CH})_2\text{COCH}_3$ ), 6.82 (d,  $J = 8.4$  Hz, 2 H,  $(\text{CH})_2\text{COCH}_2$ ), 5.59 (d,  $J = 5.4$  Hz, 1 H,  $\text{OCHO}$ ), 5.16-4.97 (masked by  $\text{CD}_3\text{OH}$ , 1 H), 4.09-4.02 (m, 2 H), 3.99-3.82 (m, 10 H), 3.88 (s, 3 H,  $\text{OCH}_3$ ), 3.52-3.32 (m, 1 H), 3.21-2.75 (m, 5 H), 2.55-2.40 (m, 1 H), 2.10-1.95 (m, 1 H), 1.75-1.25 (m, 2 H), 0.93 (d,  $J = 6.3$  Hz, 3 H,  $\text{CH}(\text{CH}_3)_2$ ), 0.88 (d,  $J = 6.6$  Hz, 3 H,  $\text{CH}(\text{CH}_3)_2$ );  $^{31}\text{P}$  NMR (121 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  19.5.

#### Example 12

Compound 16: Compound 15 (0.350 g, 0.488 mmol) was coevaporated with anhydrous pyridine (3 x 10 mL), each time filling with  $\text{N}_2$ . Residue was dissolved in anhydrous pyridine (2.5 mL) and phenol (0.459 g, 4.88 mmol) was added. This solution was heated to  $70^{\circ}\text{C}$ , then 1,3-dicyclohexylcarbodiimide (0.403 g, 1.93 mmol) was added and reaction mixture was heated at  $70^{\circ}\text{C}$  for 7 h. Reaction mixture was concentrated, coevaporated with toluene and

residue obtained was diluted with EtOAc, precipitating 1,3-dicyclohexylurea. The mixture was filtered and filtrate concentrated and residue obtained was purified (silica gel, 2% MeOH/CH<sub>2</sub>Cl<sub>2</sub>, then another column 75% EtOAc/Hex) to give a clear oil (0.1324 g, 31%).  
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.71 (d, *J* = 8.7 Hz, 2 H, SO<sub>2</sub>C(CH)<sub>2</sub>), 7.41-7.18 (m, 10 H, Ar), 7.14 (d, *J* = 8.4 Hz, 2 H, CH<sub>2</sub>C(CH)<sub>2</sub>(CH)<sub>2</sub>), 6.99 (d, *J* = 9.0 Hz, 2 H, (CH)<sub>2</sub>COCH<sub>3</sub>), 6.83 (d, *J* = 8.4 Hz, 2 H, (CH)<sub>2</sub>COCH<sub>2</sub>), 5.64 (d, *J* = 5.1 Hz, 1 H, OCHO), 5.16-4.92 (m, 2 H), 4.32-3.62 (m, 12 H), 3.87 (s, 3 H, OCH<sub>3</sub>), 3.22-2.73 (m, 7 H), 1.95-1.75 (m, 3 H), 0.93 (d, *J* = 6.6 Hz, 3 H, CH(CH<sub>3</sub>)<sub>2</sub>), 0.88 (d, *J* = 6.6 Hz, 3 H, CH(CH<sub>3</sub>)<sub>2</sub>); <sup>31</sup>P NMR (121 MHz, CDCl<sub>3</sub>): δ 14.3.

10

### Example 13

Compound 17: To a solution of compound 16 (0.132 g, 0.152 mmol) in acetonitrile (1.5 mL) at 0°C was added 1.0 M NaOH (0.38 mL, 0.381 mmol). Reaction mixture was stirred for 2 h at 0°C, then Dowex 50 (H+) resin was added until pH = 1. The resin was removed by  
15 filtration and the filtrate was concentrated and washed with EtOAc/Hex (1:2, 25 mL), then dried under high vacuum to give a clear film (0.103 g, 85%). This film was coevaporated with anhydrous pyridine (3 x 5 mL), filling with N<sub>2</sub>. The residue was dissolved in anhydrous pyridine (1 mL) and ethyl lactate (0.15 mL, 1.30 mmol) was added and reaction mixture was heated at 70°C. After 5 min, 1,3-dicyclohexylcarbodiimide (0.107 g, 0.520 mmol) was added  
20 and reaction mixture was stirred at 70°C for 2.5 h. Additional 1,3-dicyclohexylcarbodiimide (0.055 g, 0.270 mmol) was added and reaction continued for another 1.5 h. Reaction mixture was concentrated and coevaporated with toluene and diluted with EtOAc, precipitating 1,3-dicyclohexylurea. The mixture was filtered and filtrate concentrated and residue obtained was purified (silica gel, 80 to 100% EtOAc/Hex) to give a white foam (0.0607 g, 52%).  
25 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.71 (d, *J* = 8.7 Hz, 2 H, SO<sub>2</sub>C(CH)<sub>2</sub>), 7.39-7.16 (m, 5 H, Ar), 7.13 (d, *J* = 8.1 Hz, 2 H, CH<sub>2</sub>C(CH)<sub>2</sub>(CH)<sub>2</sub>), 6.99 (d, *J* = 9.0 Hz, 2 H, (CH)<sub>2</sub>COCH<sub>3</sub>), 6.82 (d, *J* = 8.4 Hz, 2 H, (CH)<sub>2</sub>COCH<sub>2</sub>), 5.64 (d, *J* = 5.1 Hz, 1 H, OCHO), 5.16-4.92 (m, 3 H), 4.35-3.65 (m, 14 H), 3.87 (s, 3 H, OCH<sub>3</sub>), 3.22-2.73 (m, 7 H), 1.95-1.80 (m, 3 H), 1.59 (d, *J* = 6.9 Hz, 1.5 H, CCHCH<sub>3</sub>), 1.47 (d, *J* = 7.2 Hz, 1.5 H, CCHCH<sub>3</sub>), 1.37-1.18 (m, 3 H), 0.92 (d, *J* = 6.6 Hz, 3 H, CH(CH<sub>3</sub>)<sub>2</sub>), 0.88 (d, *J* = 6.6 Hz, 3 H, CH(CH<sub>3</sub>)<sub>2</sub>); <sup>31</sup>P NMR (121 MHz, CDCl<sub>3</sub>): δ 19.2, 17.2.

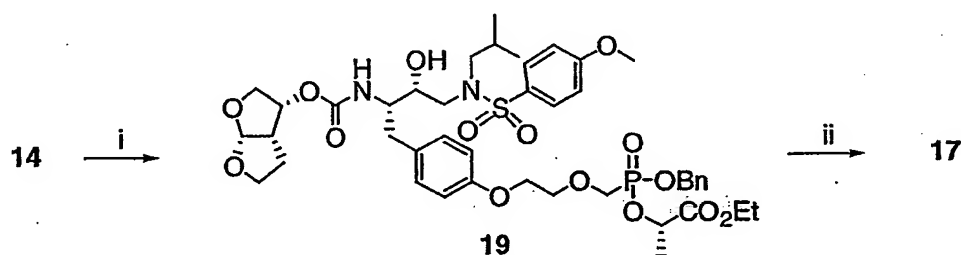
30

**Example 14**

Compound 18: Compound 17 (11.5 mg, 0.013 mmol) was dissolved in DMSO (0.14 mL) and acetonitrile (0.29 mL). PBS (pH 7.4, 1.43 mL) was added slowly with stirring. Porcine liver esterase (Sigma, 0.1 mL) was added and reaction mixture was gently stirred at 38°C.

- 5 After 24 h, additional porcine liver esterase (0.1 mL) and DMSO (0.14 mL) were added and reaction mixture stirred for 48 h at 38°C. Reaction mixture concentrated and methanol was added to precipitate the enzyme. The mixture was filtered, concentrated and purified by reverse phase chromatography to give a white powder after lyophilization (7.1 mg, 69%). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.76 (d, *J* = 8.7 Hz, 2 H, SO<sub>2</sub>C(CH)<sub>2</sub>), 7.15 (d, *J* = 8.4 Hz, 2 H, CH<sub>2</sub>C(CH)<sub>2</sub>(CH)<sub>2</sub>), 7.08 (d, *J* = 9.0 Hz, 2 H, (CH)<sub>2</sub>COCH<sub>3</sub>), 6.83 (d, *J* = 8.7 Hz, 2 H, (CH)<sub>2</sub>COCH<sub>2</sub>), 5.59 (d, *J* = 5.1 Hz, 1 H, OCHO), 5.16-4.90 (masked by CD<sub>3</sub>OH, 2 H), 4.19-3.65 (m, 12 H), 3.88 (s, 3 H, OCH<sub>3</sub>), 3.50-3.27 (m, 1 H), 3.20-2.78 (m, 5 H), 2.55-2.40 (m, 1 H), 2.05-1.90 (m, 1 H), 1.75-1.30 (m, 2 H), 1.53 (d, *J* = 6.6 Hz, 3 H, CCHCH<sub>3</sub>), 0.93 (d, *J* = 6.6 Hz, 3 H, CH(CH<sub>3</sub>)<sub>2</sub>), 0.88 (d, *J* = 6.6 Hz, 3 H, CH(CH<sub>3</sub>)<sub>2</sub>); <sup>31</sup>P NMR (121 MHz, CD<sub>3</sub>OD): δ 16.7.

Alternatively, compound 17 was prepared as described below (Scheme 3).

**Scheme 3**

Reagents and conditions: i. a. 14, DABCO, tol, reflux, b. ethyl lactate, PyBOP, DIPEA, DMF, 59%; ii. a. H<sub>2</sub>, Pd/C, EtOH; b. PhOH, PyBOP, DIPEA, DMF, 35%.

Example 15

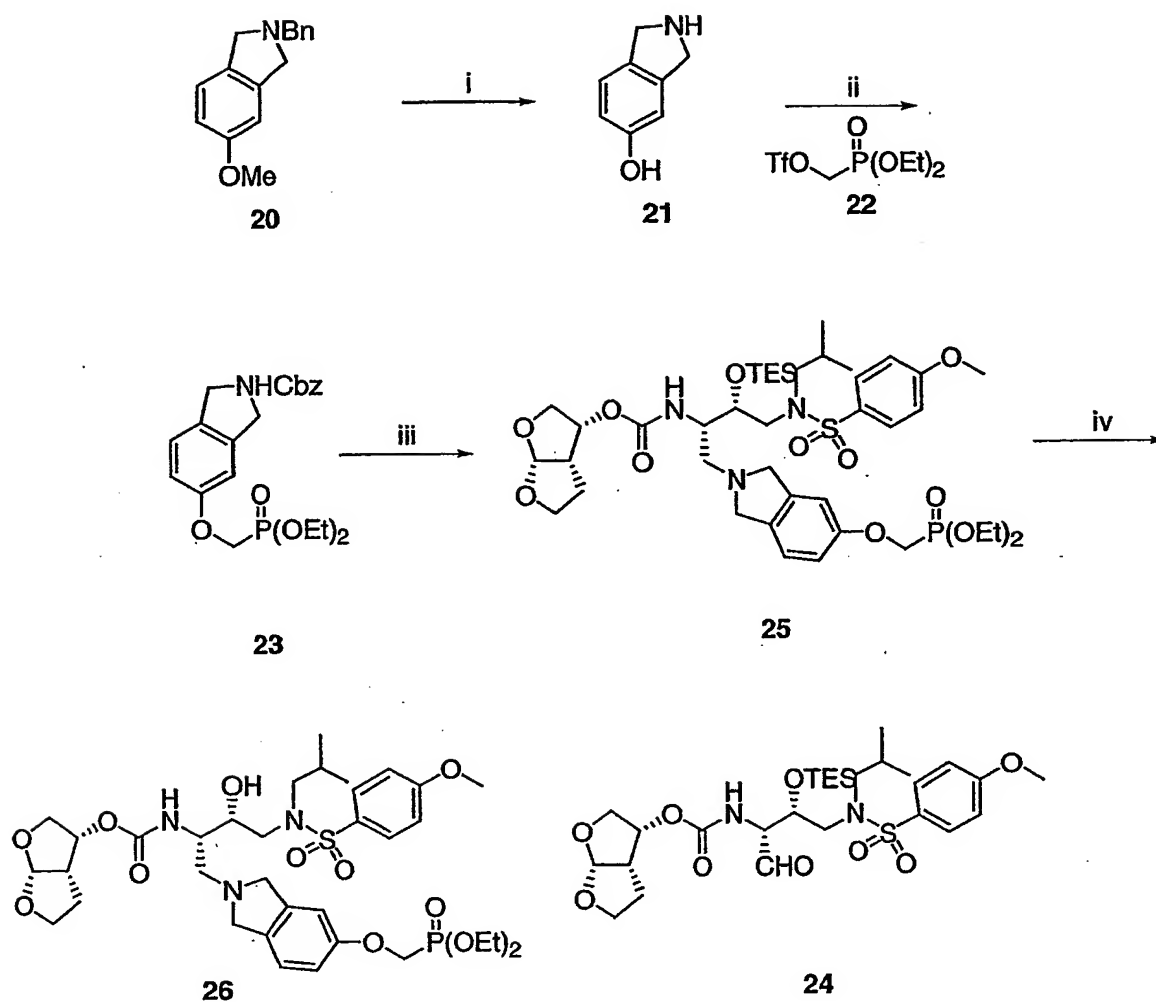
Compound 19: To a solution of compound 14 (0.945 g, 1.05 mmol) in anhydrous toluene (10.0 mL) was added 1,4-diazobicyclo[2.2.2] octane (0.130 g, 1.16 mmol) and reaction mixture was refluxed for 2 h. After cooling to room temperature, reaction mixture was diluted with EtOAc and washed with 1.0 N HCl and dried (MgSO<sub>4</sub>). Concentration gave a white foam (0.785 g, 93%). Residue was dissolved in anhydrous DMF (10.0 mL) and to this solution was added ethyl (S)-lactate (0.23 mL, 2.00 mmol) and diisopropylethylamine (0.70 mL, 4.00 mmol), followed by benzotriazol-1-yloxytripyrroldinophosphonium hexafluorophosphate (1.041 g, 2.00 mmol). Reaction mixture was stirred for 20 h, then concentrated and residue was dissolved in EtOAc and washed with 1.0 N HCl, saturated NaHCO<sub>3</sub>, brine and dried (MgSO<sub>4</sub>). Concentration and purification (silica gel, 2 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave an off-white foam (0.520 g, 59%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.72 (d, *J* = 7.5 Hz, 2 H, SO<sub>2</sub>C(CH<sub>2</sub>)<sub>2</sub>), 7.50-7.27 (m, 4 H, Ar), 7.12 (d, *J* = 8.1 Hz, 2 H, CH<sub>2</sub>C(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>), 7.00 (d, *J* = 6.6 Hz, 2 H, (CH<sub>2</sub>)<sub>2</sub>COCH<sub>3</sub>), 6.81 (d, *J* = 8.4 Hz, 2 H, (CH<sub>2</sub>)<sub>2</sub>COCH<sub>2</sub>), 5.64 (d, *J* = 5.1 Hz, 1 H, OCHO), 5.37-4.90 (m, 5 H), 4.35-3.65 (m, 14 H), 3.88 (s, 3 H, OCH<sub>3</sub>), 3.24-2.70 (m, 7 H), 1.90-1.70 (m, 3 H), 1.54 (d, *J* = 6.9 Hz, 1.5 H, CCHCH<sub>3</sub>), 1.47 (d, *J* = 6.9 Hz, 1.5 H, CCHCH<sub>3</sub>), 1.37-1.22 (m, 3 H), 0.93 (d, *J* = 6.3 Hz, 3 H, CH(CH<sub>3</sub>)<sub>2</sub>), 0.89 (d, *J* = 6.0 Hz, 3 H, CH(CH<sub>3</sub>)<sub>2</sub>); <sup>31</sup>P NMR (121 MHz, CDCl<sub>3</sub>): δ 22.3, 21.2.

Example 16

Compound 17: A mixture of compound 19 (0.520 g, 0.573 mmol) and 10% palladium on carbon (0.055 g) in ethanol (10 mL) was stirred under a hydrogen atmosphere (1 atm) for 2 h. Celite was added to the reaction mixture and stirred for 5 min, then mixture was filtered through Celite and concentrated to give a white foam (0.4649 g, 99%). Residue was dissolved in anhydrous DMF (5.0 mL) and to this solution was added phenol (0.097 g, 1.03 mmol), diisopropylethylamine (0.36 mL, 2.06 mmol) followed by benzotriazol-1-yloxytripyrroldinophosphonium hexafluorophosphate (0.536 g, 1.03 mmol). Reaction mixture was stirred for 20 h, then concentrated and residue was dissolved in EtOAc and washed with 1 N HCl, H<sub>2</sub>O, sat. NaHCO<sub>3</sub>, brine and dried (MgSO<sub>4</sub>). Concentration and purification (silica gel, 2 % MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave a white foam (0.180 g, 35%).



Scheme 4



Reagents and conditions: i. a. 48% HBr, 120°C, 65%; b. H<sub>2</sub>, Pd(OH)<sub>2</sub>, EtOH, 100%;  
 ii. CbzCl, NaOH, toluene/H<sub>2</sub>O, 0°C to rt, 43%; b. 22, CsCO<sub>3</sub>, CH<sub>3</sub>CN, 99%;  
 iii. a. H<sub>2</sub>, Pd/C, AcOH, EtOAc/EtOH, 95%; b. 24, NaBH(OAc)<sub>3</sub>, 1,2-DCE, 21%;  
 iv. 4% HF/CH<sub>3</sub>CN, 62%.

#### Example 17

- 5 Compound 21: Compound 20 (11.5 g, 48.1 mmol) in 48% HBr (150 mL) was heated at 120°C for 4 h, then cooled to room temperature and diluted with EtOAc. Mixture was neutralized with saturated NaHCO<sub>3</sub> solution and solid NaHCO<sub>3</sub> and extracted with EtOAc containing MeOH. Organic layer dried (MgSO<sub>4</sub>), concentrated, and purified (silica gel, 1:2

EtOAc/Hex with 1% MeOH) to give a brown solid (7.0 g, 65%). The resulting compound (7.0 g, 31.1 mmol) and 10% palladium hydroxide (2.1 g) in EtOH (310 mL) was stirred under a hydrogen atmosphere for 1 d, then filtered through Celite and concentrated to give an off-white solid (4.42 g, 100%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.01 (d, *J* = 7.8 Hz, 1 H, Ar), 6.64 (s, 1 H, Ar), 6.61 (d, *J* = 8.1 Hz, 2 H, Ar), 4.07 (s, 2 H, ArCH<sub>2</sub>N), 4.05 (s, 2 H, ArCH<sub>2</sub>N).

#### Example 18

Compound 22: To a solution of compound 21 (4.42 g, 32.7 mmol) in 1.0 M NaOH (98 mL, 98.25 mmol) at 0°C was added dropwise benzyl chloroformate (7.00 mL, 49.13 mmol) in toluene (7 mL). After addition was complete, reaction mixture was stirred overnight at room temperature. Reaction mixture was diluted with EtOAc and extracted with EtOAc (3x). Combined organic layer was dried (MgSO<sub>4</sub>), concentrated and purified (silica gel, 2% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give a white solid (3.786 g, 43%). The resulting compound (0.6546 g, 2.43 mmol) was dissolved in anhydrous acetonitrile (10 mL), and compound 23 (0.782 g, 2.92 mmol) was added, followed by cesium carbonate (1.583 g, 4.86 mmol). Reaction mixture was stirred for 2h at room temperature, then filtered, concentrated, and purified (3% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give a brownish oil (1.01 g, 99%).

#### Example 19

Compound 25: To a solution of compound 22 (0.100 g, 0.238 mmol) in EtOAc/EtOH (2 mL, 1:1) was added acetic acid (14 μL, 0.238 mmol) and 10% palladium on carbon (0.020 g) and the mixture was stirred under a hydrogen atmosphere for 2 h. Celite was added to the reaction mixture and stirred for 5 min, then filtered through Celite. Concentration and drying under high vacuum gave a reddish film (0.0777 g, 95%). The resulting amine (0.0777 g, 0.225 mmol) and aldehyde 24 (0.126 g, 0.205 mmol) in 1,2-dichloroethane (1.2 mL) were stirred for 5 min at 0°C, then sodium triacetoxyborohydride (0.0608 g, 0.287 mmol) was added. Reaction mixture was stirred for 1 h at 0°C, then quenched with saturated NaHCO<sub>3</sub> solution and brine. Extracted with EtOAc, the organic layer was dried (MgSO<sub>4</sub>), concentrated and purified (silica gel, 2% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give a brown foam (38.7 mg, 21%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.74 (d, *J* = 8.7 Hz, 2 H, Ar), 7.09 (d, *J* = 8.7 Hz, 1 H, Ar), 7.05-6.72 (m, 4 H, Ar), 5.71 (d, *J* = 5.1 Hz, 1 H), 5.22-5.07 (m, 2 H), 4.22-4.17 (m, 7 H),

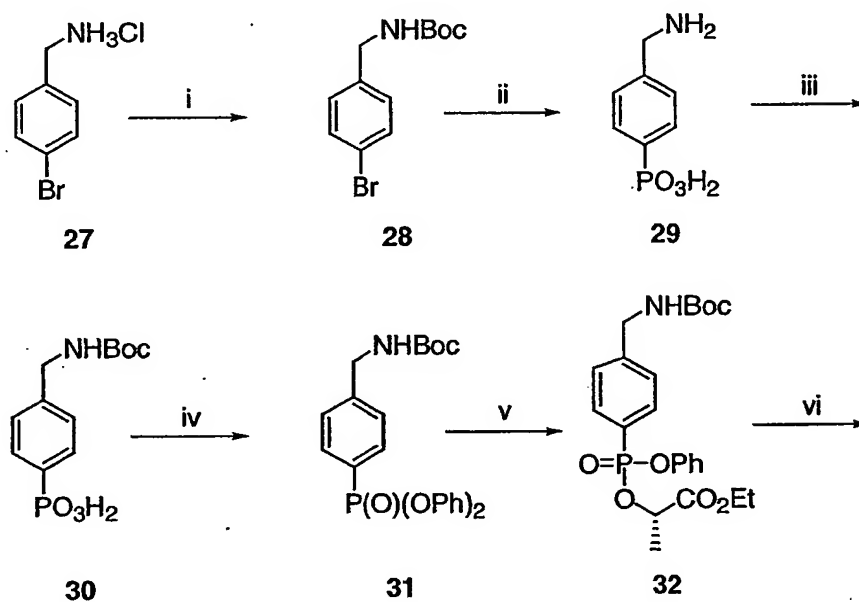
4.16-3.69 (m, 9 H), 3.82 (s, 3 H), 3.25-2.51 (m, 7 H), 2.22-1.70 (m, 3 H), 1.37 (t,  $J = 6.9$  Hz, 6 H), 1.10-0.58 (m, 21 H);  $^{31}\text{P}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  19.5.

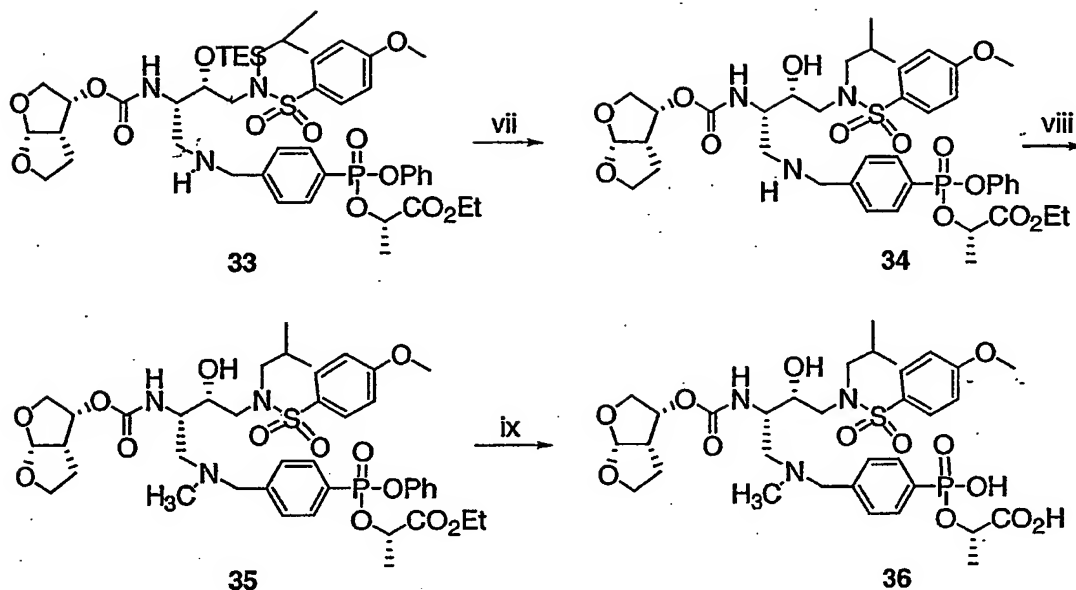
### Example 20

- 5 Compound 26: To a solution of compound 25 (38.7 mg, 0.0438 mmol) in acetonitrile (0.5 mL) at  $0^\circ\text{C}$  was added 48% HF (0.02 mL). The reaction mixture was stirred at room temperature for 2 h, then quenched with saturated  $\text{NaHCO}_3$  solution and extracted with EtOAc. Organic layer was separated, dried ( $\text{MgSO}_4$ ), concentrated and purified (silica gel, 3 to 5% MeOH/ $\text{CH}_2\text{Cl}_2$ ) to give a red film (21.2 mg, 62%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$
- 10 7.73 (d,  $J = 8.7$  Hz, 2 H, Ar), 7.10 (d,  $J = 8.7$  Hz, 1 H, Ar), 6.97 (d,  $J = 8.70$  Hz, 2 H), 6.90-6.76 (m, 2 H), 5.72 (d,  $J = 5.1$  Hz, 1 H), 5.41 (d,  $J = 9.0$  Hz, 1 H), 5.15 (q,  $J = 6.6$  Hz, 1 H), 4.38-4.17 (m, 7 H), 4.16-3.65 (m, 9 H), 3.87 (s, 3 H), 3.20-2.82 (m, 7 H), 2.75-1.79 (m, 3 H), 1.37 (t,  $J = 6.9$  Hz, 6 H), 0.90 (d,  $J = 6.6$  Hz, 3 H), 0.88 (d,  $J = 6.6$  Hz, 3 H);  $^{31}\text{P}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  19.3.

15

Scheme 5





Reagents and conditions: i.  $\text{Boc}_2\text{O}$ ,  $\text{NaOH}$ ,  $\text{H}_2\text{O}$ , 96%;  
 ii. a.  $\text{HP}(\text{OEt})_2$ ,  $\text{Et}_3\text{N}$ ,  $(\text{PPh}_3)_4\text{Pd}$ ,  $90^\circ\text{C}$ , b.  $\text{TMSBr}$ ,  $\text{CH}_3\text{CN}$ , 65%;  
 iii.  $\text{Boc}_2\text{O}$ ,  $\text{NaOH}$ ,  $\text{THF}/\text{H}_2\text{O}$ , 89%; iv.  $\text{PhOH}$ ,  $\text{DCC}$ ,  $\text{pyr}$ ,  $70^\circ\text{C}$ , 71%;  
 v. a.  $\text{NaOH}$ ,  $\text{CH}_3\text{CN}$ , 94%; b.  $\text{Et lactate}$ ,  $\text{DCC}$ ,  $\text{pyr}$ ,  $70^\circ\text{C}$ , 80%; vi. a.  $\text{TFA}$ ,  $\text{CH}_2\text{Cl}_2$ ;  
 b. 24,  $\text{AcOH}$ ,  $\text{NaBH}_3\text{CN}$ ,  $\text{EtOH}$ , 33%; vii. 4%  $\text{HF}/\text{CH}_3\text{CN}$ , 88%;  
 viii.  $\text{HCHO}$ ,  $\text{AcOH}$ ,  $\text{NaBH}_3\text{CN}$ ,  $\text{EtOH}$ , 67%;  
 ix.  $\text{CH}_3\text{CN}$ ,  $\text{DMSO}$ ,  $\text{PBS}$ , porcine liver esterase,  $38^\circ\text{C}$ , 21%.

### Example 21

Compound 28: To a mixture of 4-bromobenzylamine hydrochloride (15.23 g, 68.4 mmol) in  
 5  $\text{H}_2\text{O}$  (300 mL) was added sodium hydroxide (8.21 g, 205.2 mmol), followed by di-*tert*-butyl  
 dicarbonate (16.45g, 75.3 mmol). Reaction mixture was vigorously stirred for 18 h, then  
 diluted with  $\text{EtOAc}$  (500 mL). Organic layer separated and aqueous layer extracted with  
 $\text{EtOAc}$  (200 mL). Combined organic layer was dried ( $\text{MgSO}_4$ ), concentrated and dried under  
 high vacuum to give a white solid (18.7 g, 96%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.41 (d,  $J$  =  
 10 8.4 Hz, 2 H), 7.12 (d,  $J$  = 8.3 Hz, 2 H), 4.82 (s, 1 H,  $\text{NH}$ ), 4.22 (d,  $J$  = 6.1 Hz, 2 H), 1.41 (s, 9  
 H).

### Example 22

Compound 29: Compound 28 (5.00 g, 17.47 mmol) was coevaporated with toluene. Diethyl  
 15 phosphite (11.3 mL, 87.36 mmol) was added and mixture was coevaporated with toluene

(2x). Triethylamine (24.0 mL, 174.7 mmol) was added and mixture was purged with argon for 10 min, then tetrakis(triphenylphosphine) palladium(0) (4.00 g, 3.49 mmol) was added. Reaction mixture was refluxed for 18 h, cooled, concentrated and diluted with EtOAc. Washed with 0.5 N HCl, 0.5 M NaOH, H<sub>2</sub>O, brine and dried (MgSO<sub>4</sub>). Concentrated and purification (silica gel, 70% EtOAc/Hex) gave an impure reaction product as a yellow oil (6.0 g). This material (6.0 g) was dissolved in anhydrous acetonitrile (30 mL) and cooled to 0°C. Bromotrimethylsilane (11.5 mL, 87.4 mmol) was added and reaction mixture was warmed to room temperature over 15 h. Reaction mixture was concentrated, dissolved in MeOH (50 mL) and stirred for 1.5 h. H<sub>2</sub>O (1 mL) was added and mixture stirred for 2 h. Concentrated to dryness and dried under high vacuum, then triturated with Et<sub>2</sub>O containing 2% MeOH to give a white solid (3.06 g, 65 %). <sup>1</sup>H NMR (300 MHz, D<sub>2</sub>O): δ 7.67 (dd, *J* = 12.9, 7.6 Hz, 2 H), 7.45-7.35 (m, 2 H), 4.10 (s, 2 H); <sup>31</sup>P NMR (121 MHz, D<sub>2</sub>O): δ 12.1.

#### Example 23

Compound 30: Compound 29 (4.78 g, 17.84 mmol) was dissolved in H<sub>2</sub>O (95 mL) containing sodium hydroxide (3.57 g, 89.20 mmol). Di-*tert*-butyl dicarbonate (7.63 g, 34.94 mmol) was added, followed by THF (25 mL). The clear reaction mixture was stirred overnight at room temperature then concentrated to ~100 mL. Washed with EtOAc and acidified to pH 1 with 1 N HCl and extracted with EtOAc (7x). Combined organic layer was dried (MgSO<sub>4</sub>), concentrated and dried under high vacuum. Trituration with Et<sub>2</sub>O gave a white powder (4.56 g, 89%). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.85-7.71 (m, 2 H), 7.39-7.30 (m, 2 H), 4.26 (s, 2 H), 1.46 (s, 9 H); <sup>31</sup>P NMR (121 MHz, CD<sub>3</sub>OD): δ 16.3.

#### Example 24

Compound 31: Compound 30 (2.96 g, 10.32 mmol) was coevaporated with anhydrous pyridine (3 x 10 mL). To this residue was added phenol (9.71 g, 103.2 mmol) and mixture was coevaporated with anhydrous pyridine (2 x 10 mL). Pyridine (50 mL) was added and solution heated to 70°C. After 5 min, 1,3-dicyclohexylcarbodiimide (8.51 g, 41.26 mmol) was added and resulting mixture was stirred for 8 h at 70°C. Reaction mixture was cooled and concentrated and coevaporated with toluene. Residue obtained was diluted with EtOAc and the resulting precipitate was removed by filtration. The filtrate was concentrated and purified (silica gel, 20 to 40% EtOAc/Hex, another column 30 to 40% EtOAc/Hex) to give a

white solid (3.20 g, 71%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.90 (dd,  $J = 13.8, 8.2$  Hz, 2 H), 7.41-7.10 (m, 14 H), 5.17 (br s, 1 H, NH), 4.35 (d,  $J = 5.2$  Hz, 2 H), 1.46 (s, 9 H);  $^{31}\text{P}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  11.8.

5 Example 25

Compound 32: To a solution of compound 31 (3.73 g, 8.49 mmol) in acetonitrile (85 mL) at  $0^\circ\text{C}$  was added 1 M NaOH (21.2 mL, 21.21 mmol). Reaction mixture was stirred at  $0^\circ\text{C}$  for 30 min, then warmed to room temperature over 4 h. Reaction mixture cooled to  $0^\circ\text{C}$  and Dowex ( $\text{H}^+$ ) residue was added to pH 2. Mixture was filtered, concentrated and residue  
10 obtained was triturated with EtOAc/Hex (1:2) to give a white powder (2.889 g, 94%). This compound (2.00 g, 5.50 mmol) was coevaporated with anhydrous pyridine (3 x 10 mL). The residue was dissolved in anhydrous pyridine (30 mL) and ethyl (S)-lactate (6.24 mL, 55 mmol) and reaction mixture was heated to  $70^\circ\text{C}$ . After 5 min, 1,3-dicyclocarbodiimide (4.54 g, 22.0 mmol) was added. Reaction mixture was stirred at  $70^\circ\text{C}$  for 5 h, then cooled and  
15 concentrated. Residue was dissolved in EtOAc and precipitate was removed by filtration. The filtrate was concentrated and purified (25 to 35% EtOAc/Hex, another column 40% EtOAc/Hex) to give a colorless oil (2.02 g, 80%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.96-7.85 (m, 2 H), 7.42-7.35 (m, 2 H), 7.35-7.08 (m, 4 H), 5.16-5.00 (m, 1 H), 4.93 (s, 1 H, NH), 4.37 (d,  $J = 5.5$  Hz, 1 H), 4.21 (q,  $J = 7.3$  Hz, 1 H), 4.11 (dq,  $J = 5.7, 2.2$  Hz, 1 H), 1.62-1.47 (m, 3  
20 H), 1.47 (s, 9 H), 1.27 (t,  $J = 7.3$  Hz, 1.5 H), 1.17 (t,  $J = 7.3$  Hz, 1.5 H);  $^{31}\text{P}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  16.1, 15.0.

Example 26

Compound 33: Compound 32 (2.02 g, 4.36 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (41 mL) and  
25 cooled to  $0^\circ\text{C}$ . To this solution was added trifluoroacetic acid (3.5 mL) and reaction mixture was stirred at  $0^\circ\text{C}$  for 1 h, then at room temperature for 3 h. Reaction mixture was concentrated, coevaporated with EtOAc and diluted with  $\text{H}_2\text{O}$  (400 mL). Mixture was neutralized with Amberlite IRA-67 weakly basic resin, then filtered and concentrated. Coevaporation with MeOH and dried under high vacuum to give the TFA amine salt as a  
30 semi-solid (1.48 g, 94%). To a solution of the amine (1.48 g, 4.07 mmol) in absolute ethanol (20 mL) at  $0^\circ\text{C}$  was added aldehyde 24 (1.39 g, 2.26 mmol), followed by acetic acid (0.14 mL, 2.49 mmol). After stirring for 5 min, sodium cyanoborohydride (0.284 g, 4.52 mmol)

was added and reaction mixture stirred for 30 min at 0°C. Reaction was quenched with saturated NaHCO<sub>3</sub> solution and diluted with EtOAc and H<sub>2</sub>O. Aqueous layer was extracted with EtOAc (3x) and combined organic layer was dried (MgSO<sub>4</sub>), concentrated and purified (silica gel, 2 to 4% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give white foam (0.727 g, 33%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.98-7.86 (m, 2 H), 7.71 (d, *J* = 8.6 Hz, 2 H), 7.49 (br s, 2 H), 7.38-7.05 (m, 5 H), 6.98 (d, *J* = 8.8 Hz, 2 H), 5.72 (d, *J* = 5.1 Hz, 1 H), 5.28-5.00 (m, 2 H), 4.30-3.72 (m, 12 H), 3.42-3.58 (m, 1 H), 3.20-2.68 (m, 7 H), 2.25-1.42 (m, 6 H), 1.26 (t, *J* = 7.2 Hz, 1.5 H), 1.17 (t, *J* = 7.2 Hz, 1.5 H), 1.08-0.50 (m, 21 H); <sup>31</sup>P NMR (121 MHz, CDCl<sub>3</sub>): δ 16.1, 15.1.

#### 10 Example 27

Compound 34: To a solution of compound 33 (0.727 g, 0.756 mmol) in acetonitrile (7.6 mL) at 0°C was added 48% hydrofluoric acid (0.152 mL) and reaction mixture was stirred for 40 min at 0°C, then diluted with EtOAc and H<sub>2</sub>O. Saturated NaHCO<sub>3</sub> was added and aqueous layer was extracted with EtOAc (2x). Combined organic layer was dried (MgSO<sub>4</sub>), concentrated and purified (silica gel, 4 to 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give a colorless foam (0.5655 g, 88%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.95-7.82 (m, 2 H), 7.67 (d, *J* = 8.1 Hz, 2 H), 7.41 (br s, 2 H), 7.38-7.05 (m, 5 H), 6.95 (d, *J* = 7.2 Hz, 2 H), 5.76 (d, *J* = 7.9 Hz, 1 H), 5.67 (d, *J* = 5.0 Hz, 1 H), 5.32-4.98 (m, 2 H), 4.25-3.75 (m, 13 H), 3.25-2.70 (m, 7 H), 2.15-1.76 (m, 3 H), 1.53-1.41 (m, 3 H), 1.25-1.08 (m, 3 H), 0.87 (d, *J* = 4.2 Hz, 6 H); <sup>31</sup>P NMR (121 MHz, CDCl<sub>3</sub>): δ 16.1, 15.0.

#### Example 28

Compound 35: To a solution of compound 33 (0.560 g, 0.660 mmol) in absolute ethanol (13 mL) at 0°C was added 37% formaldehyde (0.54 mL, 6.60 mmol), followed by acetic acid (0.378 mL, 6.60 mmol). The reaction mixture was stirred at 0°C for 5 min, then sodium cyanoborohydride (0.415 g, 6.60 mmol) was added. Reaction mixture was warmed to room temperature over 2 h, then quenched with saturated NaHCO<sub>3</sub> solution. EtOAc was added and mixture was washed with brine. Aqueous layer was extracted with EtOAc (2x) and combined organic layer was dried (MgSO<sub>4</sub>), concentrated and purified (silica gel, 3% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give a white foam (0.384 g, 67%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.95-7.82 (m, 2 H), 7.71 (d, *J* = 8.4 Hz, 2 H), 7.38 (br s, 2 H), 7.34-7.10 (m, 5 H), 6.98 (d, *J* = 8.8 Hz, 2 H), 5.72 (d, *J* = 5.0 Hz, 1 H), 5.50 (br s, 1 H), 5.19-5.01 (m, 2 H), 4.29-3.75 (m, 10 H),

3.85 (s, 3 H), 3.35-2.70 (m, 7 H), 2.23 (s, 3 H), 2.17-1.79 (m, 3 H), 1.54 (d,  $J = 6.9$  Hz, 1.5 H), 1.48 (d,  $J = 6.8$  Hz, 1.5 H), 1.25 (t,  $J = 7.2$  Hz, 1.5 H), 1.16 (t,  $J = 7.2$  Hz, 1.5 H), 0.92 (d,  $J = 6.6$  Hz, 3 H), 0.87 (d,  $J = 6.6$  Hz, 3 H).  $^{31}\text{P}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  16.0, 14.8.

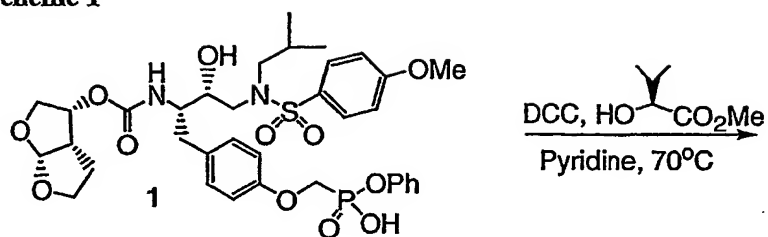
5 Example 29

Compound 36: To a solution of compound 35 (44 mg, 0.045 mmol) in acetonitrile (1.0 mL) and DMSO (0.5 mL) was added phosphate buffered saline (pH 7.4, 5.0 mL) to give a cloudy white suspension. Porcine liver esterase (200  $\mu\text{L}$ ) was added and reaction mixture was stirred for 48 h at 38°C. Additional esterase (600  $\mu\text{L}$ ) was added and reaction was continued for 4 d.

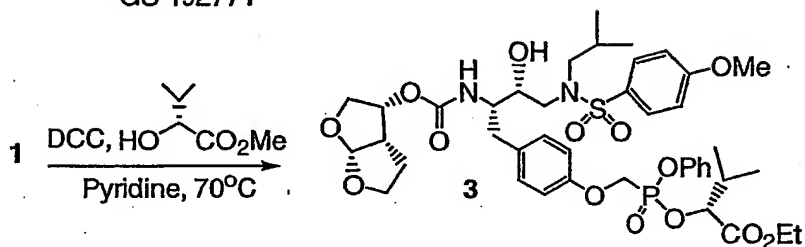
- 10 Reaction mixture was concentrated, diluted with MeOH and the resulting precipitate removed by filtration. Filtrate was concentrated and purified by reverse phase HPLC to give a white powder after lyophilization (7.2 mg, 21%).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.95 (br s, 2 H), 7.76 (d,  $J = 8.4$  Hz, 2 H), 7.64 (br s, 2 H), 7.13 (d,  $J = 8.7$  Hz, 2 H), 5.68 (d,  $J = 5.1$  Hz, 1 H), 5.14 (br s, 1 H), 4.77 (br s, 1 H), 4.35-3.59 (m, 8 H), 3.89 (s, 3 H), 3.45-2.62 (m, 10 H), 2.36-  
15 1.86 (m, 3 H), 1.44 (d,  $J = 6.3$  Hz, 3 H), 0.92 (d,  $J = 6.6$  Hz, 3 H), 0.84 (d,  $J = 6.6$  Hz, 3 H);  $^{31}\text{P}$  NMR (121 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  13.8.



## Scheme 1

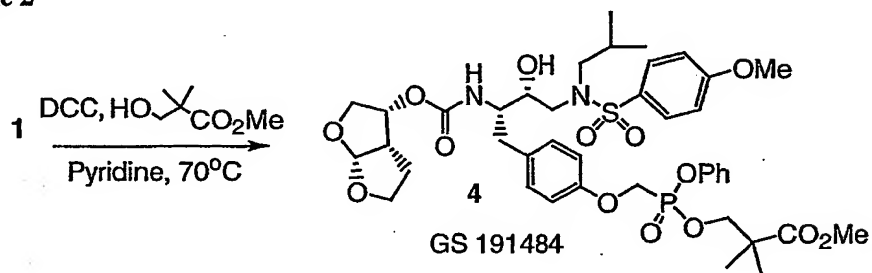


GS 192771

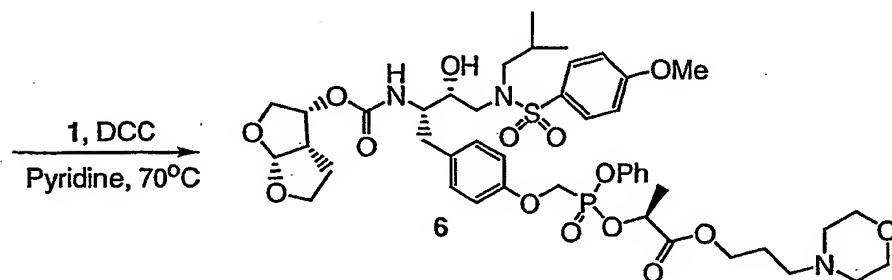
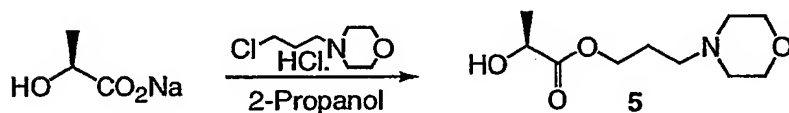


GS 192772

## Scheme 2

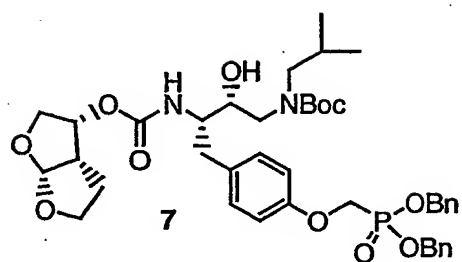


GS 191484




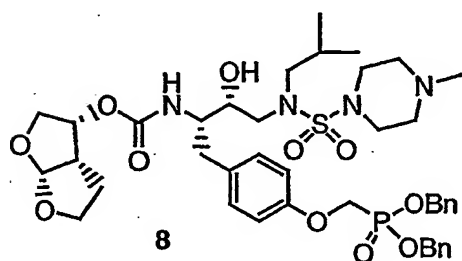
GS 192781

Scheme 3



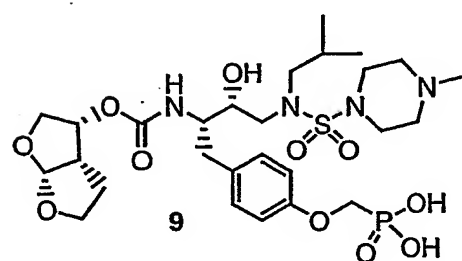
(1) TFA, CH<sub>2</sub>Cl<sub>2</sub>

(2) TEA, -SO<sub>2</sub>Cl

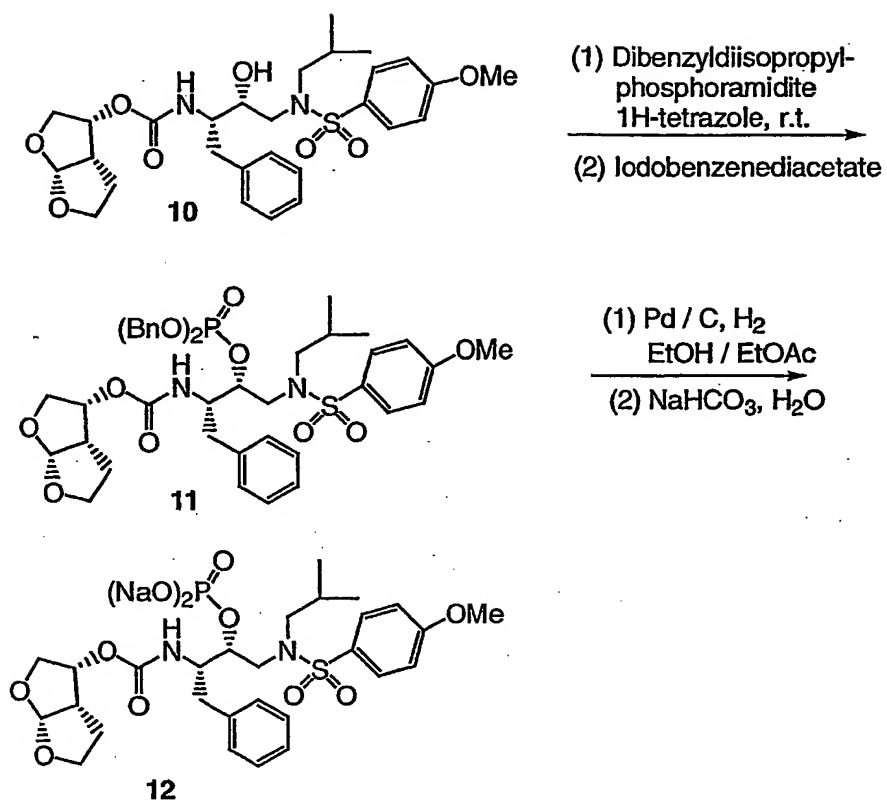


Pd / C, H<sub>2</sub>, r.t.

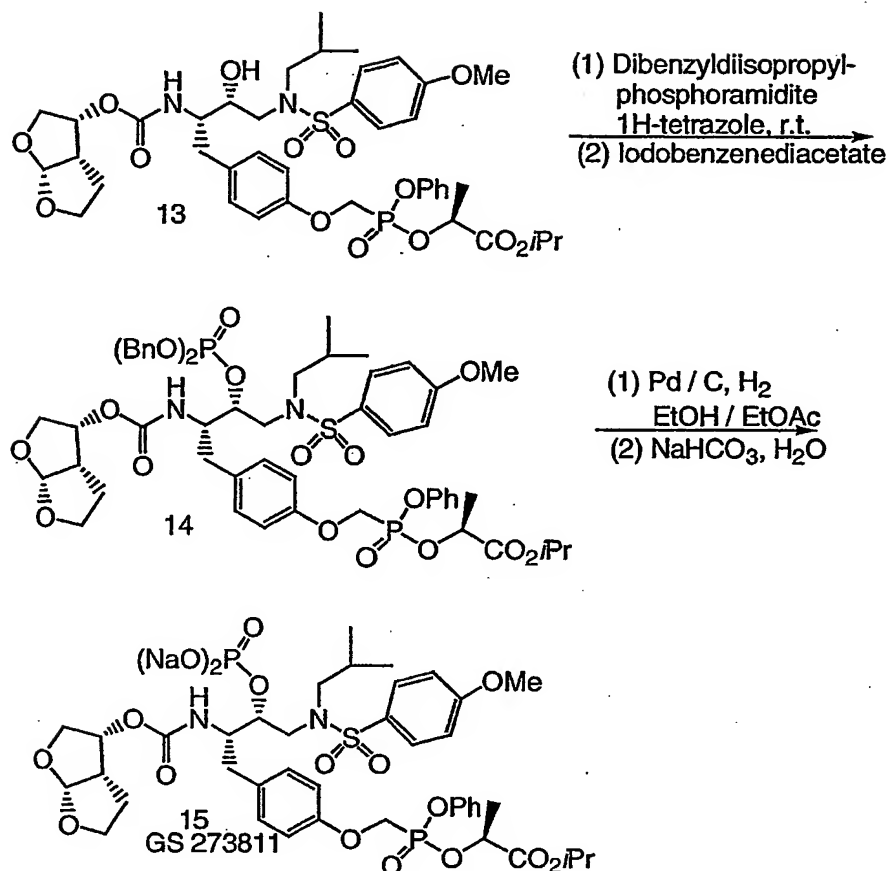
EtOAc, 2-propanol



## Scheme 4



## Scheme 5

5 Example 1

Monophospholactate 2: A solution of 1 (0.11 g, 0.15 mmol) and  $\alpha$ -hydroxyisovaleric acid ethyl-(S)-ester (71 mg, 0.49 mmol) in pyridine (2 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (0.10 g, 0.49 mmol) was added. The reaction mixture was stirred at 70°C for 2 h and cooled to room temperature. The solvent was removed under reduced pressure. The residue was suspended in EtOAc and 1,3-dicyclohexyl urea was filtered off. The product was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with 0.2 N HCl, H<sub>2</sub>O, saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the monophospholactate (35 mg, 28%, GS 192771, 1/1 diastereomeric mixture) as a white solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.71 (d, J = 8.7 Hz, 2H), 7.36-7.14 (m, 7H), 6.99 (d, J = 8.7 Hz, 2H), 6.94-6.84 (dd, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.00-4.85 (m, 3H), 4.55 (dd, 1H), 4.41 (dd, 1H), 4.22-4.07 (m, 2H), 3.96-3.68 (m, 9H), 3.12-2.74 (m, 7H), 2.29 (m, 1H), 1.85-1.57

(m, 3H), 1.24 (m, 3H), 1.05 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H), 0.9 (m, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.7, 15.1.

### Example 2

- 5 Monophospholactate 3: A solution of 1 (0.11 g, 0.15 mmol) and  $\alpha$ -hydroxyisovaleric acid ethyl-(R)-ester (71 mg, 0.49 mmol) in pyridine (2 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (0.10 g, 0.49 mmol) was added. The reaction mixture was stirred at 70°C for 2 h and cooled to room temperature. The solvent was removed under reduced pressure. The residue was suspended in EtOAc and 1,3-dicyclohexyl urea was filtered off.
- 10 The product was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with 0.2 N HCl,  $\text{H}_2\text{O}$ , saturated NaCl, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the monophospholactate (35 mg, 28%, GS 192772, 1/1 diastereomeric mixture) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71 (d, J = 8.7 Hz, 2H), 7.35-7.13 (m, 7H), 6.98 (d, J = 8.7
- 15 Hz, 2H), 6.93-6.83 (dd, 2H), 5.64 (d, J = 5.4 Hz, 1H), 5.04-4.85 (m, 3H), 4.54 (dd, 1H), 4.39 (dd, 1H), 4.21-4.06 (m, 2H), 3.97-3.67 (m, 9H), 3.12-2.75 (m, 7H), 2.27 (m, 1H), 1.83-1.57 (m, 3H), 1.26 (m, 3H), 1.05 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H), 0.9 (m, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.7, 15.1.

### 20 Example 3

- Monophospholactate 4: A solution of 1 (0.10 g, 0.13 mmol) and methyl-2,2-dimethyl-3-hydroxypropionate (56  $\mu\text{L}$ , 0.44 mmol) in pyridine (1 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (91 mg, 0.44 mmol) was added. The reaction mixture was stirred at 70°C for 2 h and cooled to room temperature. The solvent was removed under reduced
- 25 pressure. The residue was suspended in EtOAc and 1,3-dicyclohexyl urea was filtered off. The product was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with 0.2 N HCl,  $\text{H}_2\text{O}$ , saturated NaCl, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the monophospholactate (72 mg, 62%, GS 191484) as a white solid:  $^1\text{H}$  NMR
- 30 ( $\text{CDCl}_3$ )  $\delta$  7.71 (d, J = 8.7 Hz, 2H), 7.34 (m, 2H), 7.25-7.14 (m, 5H), 7.00 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.05 (m, 2H), 4.38 (d, J = 9.6 Hz, 2H),

4.32-4.20 (m, 2H), 4.00 (m, 2H), 3.87-3.63 (m, 12H), 3.12-2.78 (m, 7H), 1.85-1.67 (m, 3H), 1.20 (m, 6H), 0.91 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  16.0.

#### Example 4

- 5 Lactate 5: To a suspension of lactic acid sodium salt (5 g, 44.6 mmol) in 2-propanol (60 mL) was added 4-(3-chloropropyl)morpholine hydrochloride (8.30 g, 44.6 mmol). The reaction mixture was heated to reflux for 18 h and cooled to room temperature. The solid was filtered and the filtrate was recrystallized from EtOAc / hexane to give the lactate (1.2 g, 12%).

#### 10 Example 5

- Monophospholactate 6: A solution of 1 (0.10 g, 0.13 mmol) and lactate 5 (0.10 g, 0.48 mmol) in pyridine (2 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (0.10 g, 0.49 mmol) was added. The reaction mixture was stirred at 70°C for 2 h and cooled to room temperature. The solvent was removed under reduced pressure. The residue was suspended in EtOAc and 1,3-dicyclohexyl urea was filtered off. The product was partitioned between EtOAc and  $\text{H}_2\text{O}$ . The EtOAc layer was washed with saturated NaCl, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The crude product was purified by column chromatography on silica gel (4% 2-propanol/ $\text{CH}_2\text{Cl}_2$ ) to give the monophospholactate (30 mg, 24%, GS 192781, 1/1 diastereomeric mixture) as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.71 (d, J = 8.7 Hz, 2H), 7.38-7.15 (m, 7H), 7.00 (d, J = 8.7 Hz, 2H), 6.91 (m, 2H), 5.65 (d, J = 3.3 Hz, 1H), 5.18-4.98 (m, 3H), 4.54 (dd, 1H), 4.42 (dd, 1H), 4.2 (m, 2H), 4.00-3.67 (m, 16H), 3.13-2.77 (m, 7H), 2.4 (m, 5H), 1.85-1.5 (m, 5H), 1.25 (m, 2H), 0.93 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ )  $\delta$  17.4, 15.4.

#### 25 Example 6

- Sulfonamide 8: A solution of dibenzylphosphonate 7 (0.1 g, 0.13 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.5 mL) at 0°C was treated with trifluoroacetic acid (0.25 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in  $\text{CH}_2\text{Cl}_2$  (1 mL) and cooled to 0°C. Triethylamine (72  $\mu\text{L}$ , 0.52 mmol) was added followed by the treatment of 4-methylpiperazinylsulfonyl chloride (25 mg, 0.13 mmol). The solution was stirred for 1 h at

0°C and the product was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O. The organic phase was washed with saturated NaCl, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (5% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the sulfonamide 8 (32 mg, 30%, GS 273835) as a white solid:

- 5 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.35 (m, 10H), 7.11 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.2-4.91 (m, 4H), 4.2 (d, J = 10.2 Hz, 2H), 4.0-3.69 (m, 6H), 3.4-3.19 (m, 5H), 3.07-2.75 (m, 5H), 2.45 (m, 4H), 2.3 (s, 3H), 1.89-1.44 (m, 7H), 0.93 (m, 6H); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ 20.3.

10 Example 7

Phosphonic Acid 9: To a solution of 8 (20 mg, 0.02 mmol) in EtOAc (2 mL) and 2-propanol (0.2 mL) was added 10% Pd/C (5 mg). The suspension was stirred under H<sub>2</sub> atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (10 mg, 64%) as a white solid.

Example 8

- Dibenzylphosphonate 11: A solution of 10 (85 mg, 0.15 mmol) and 1H-tetrazole (14 mg, 0.20 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was treated with Dibenzyl-diisopropylphosphoramidite (60 μL, 0.20 mmol) and stirred at room temperature overnight. The product was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude product was purified by column chromatography to give the intermediate dibenzylphosphite (85 mg, 0.11 mmol) which was dissolved in CH<sub>3</sub>CN (2 mL) and treated with iodobenzenediacetate (51 mg, 0.16 mmol). The reaction mixture was stirred at room temperature for 3 h and concentrated.
- 25 The residue was partitioned between EtOAc and NaHCO<sub>3</sub>. The organic layer was washed with H<sub>2</sub>O, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the dibenzylphosphonate (45 mg, 52%) as a white solid.

30 Example 9

Disodium Salt of Phosphonic Acid 12: To a solution of 11 (25 mg, 0.03 mmol) in EtOAc (2 mL) was added 10% Pd/C (10 mg). The suspension was stirred under H<sub>2</sub> atmosphere (balloon) at room temperature for 4 h. The reaction mixture was filtered through a plug of

celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid which was dissolved in H<sub>2</sub>O (1 mL) and treated with NaHCO<sub>3</sub> (2.53 mg, 0.06 mmol). The reaction mixture was stirred at room temperature for 1 h and lyophilized overnight to give the disodium salt of phosphonic acid (19.77 mg, 95%, GS 273777) as a white solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.81 (d, J = 9.0 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 7.27-7.09 (m, 5H), 5.57 (d, J = 5.1 Hz, 1H), 5.07 (m, 1H), 4.87-4.40 (m, 3H), 3.93-3.62 (m, 6H), 3.45-2.6 (m, 6H), 2.0 (m, 2H), 1.55 (m, 1H), 0.95-0.84 (m, 6H).

#### Example 10

10 Dibenzylphosphonate 14: A solution of 13 (0.80 g, 0.93 mmol) and 1H-tetrazole (98 mg, 1.39 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) was treated with dibenzyl-diisopropylphosphoramidite (0.43 mL, 1.39 mmol) and stirred at room temperature overnight. The product was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude product was purified by column chromatography to give the intermediate dibenzylphosphite (0.68 g, 15 67%). To a solution of the dibenzylphosphite (0.39 g, 0.35 mmol) in CH<sub>3</sub>CN (5 mL) was added iodobenzenediacetate (0.17 g, 0.53 mmol). The reaction mixture was stirred at room temperature for 2 h and concentrated. The residue was partitioned between EtOAc and NaHCO<sub>3</sub>. The organic layer was washed with H<sub>2</sub>O, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 20 2-propanol/CH<sub>2</sub>Cl<sub>2</sub>) to give the dibenzylphosphonate (0.35 g, 88%) as a white solid.

#### Example 11

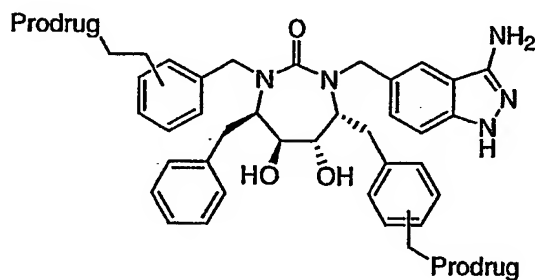
Disodium Salt of Phosphonic Acid 15: To a solution of 14 (0.39 g, 0.35 mmol) in EtOAc (30 mL) was added 10% Pd/C (0.10 g). The suspension was stirred under H<sub>2</sub> atmosphere 25 (balloon) at room temperature for 4 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid, which was dissolved in H<sub>2</sub>O (3 mL) and treated with NaHCO<sub>3</sub> (58 mg, 0.70 mmol). The reaction mixture was stirred at room temperature for 1 h and lyophilized overnight to give the disodium salt of phosphonic acid (0.31 g, 90%, GS 273811) as a white solid: <sup>1</sup>H NMR 30 (CD<sub>3</sub>OD) δ 7.81 (d, J = 9.0 Hz, 2H), 7.43-7.2 (m, 7H), 7.13 (d, J = 9.0 Hz, 2H), 6.9 (m, 2H), 5.55 (d, J = 4.8 Hz, 1H), 5.07 (m, 2H), 4.87 (m, 1H), 4.64-4.4 (m, 4H), 3.93-3.62 (m, 9H), 3.33-2.63 (m, 5H), 2.11 (m, 1H), 1.6-1.42 (m, 4H), 1.38-1.25 (m, 7H), 0.95 (d, J = 6.3 Hz, 3H), 0.84 (d, J = 6.3 Hz, 3H).



**Examples For The Preparation Of Cyclic Carbonyl-Like Phosphonate Protease Inhibitors (CCPPI)**

**Phosphonamidate Prodrugs**

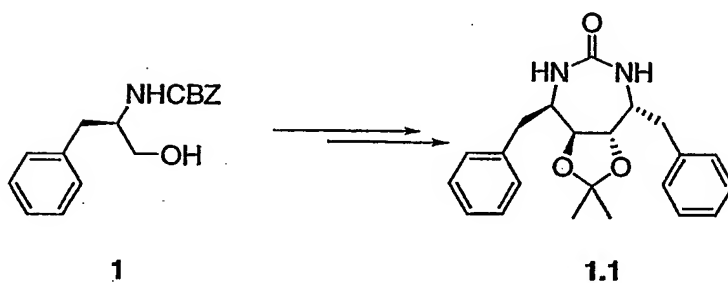
5



- Scheme 1-2                      Scaffold Synthesis  
 10    Scheme 3-10                P2'-Benzyl ether phosphonates  
       Scheme 11-13            P2'-Alkyl ether phosphonates  
       Scheme 14-17            P2'-Benzyl Amide phosphonates  
       Scheme 18-25            P1-Phosphonates  
       Scheme 50                Reagents

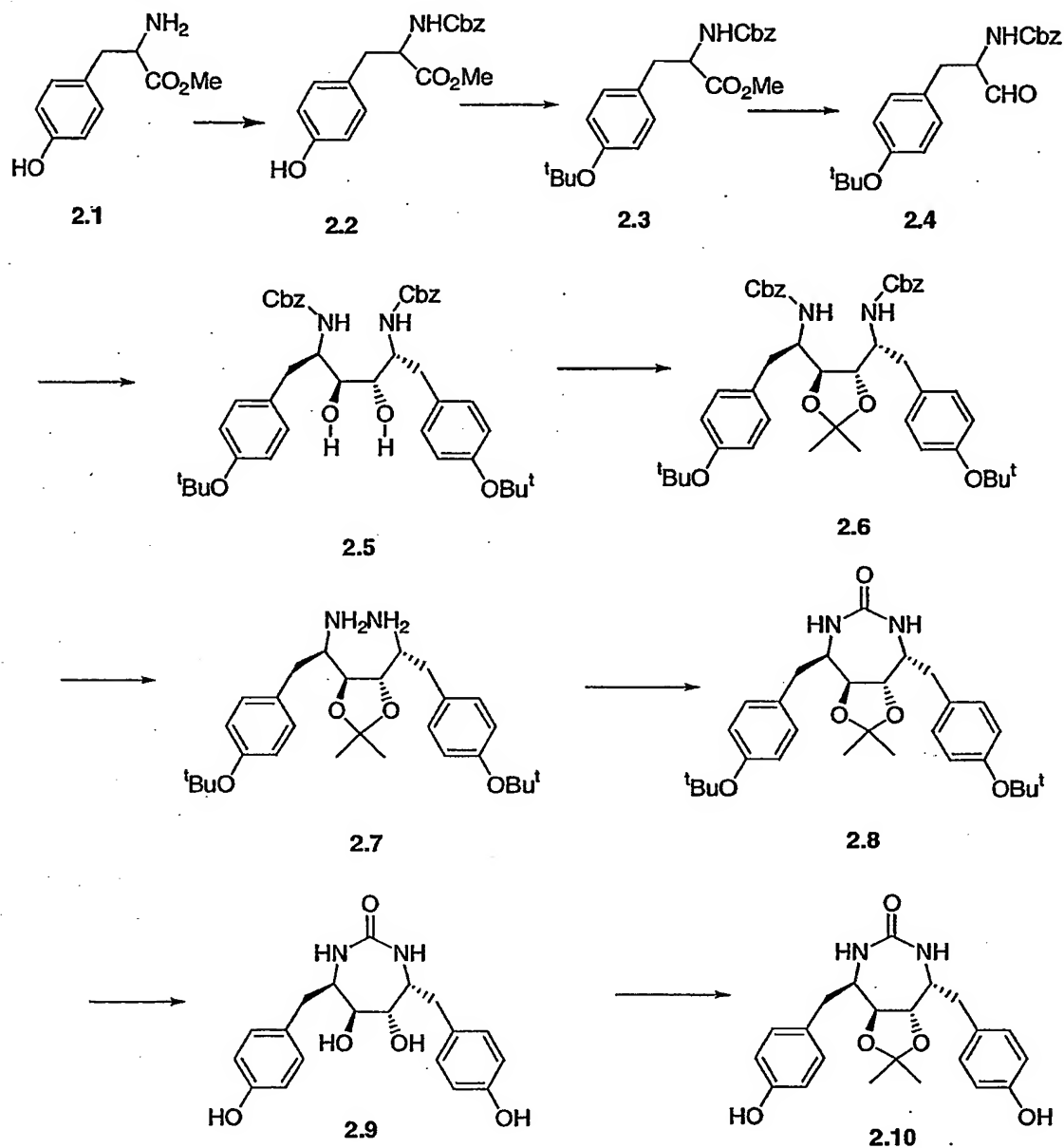
15

**Scheme 1**



The conversion of **1** to **1.1** is described in J. Org Chem 1996, 61, p444-450

Scheme 2



**2-Benzyloxycarbonylamino-3-(4-tert-butoxy-phenyl)-propionic acid methyl ester (2.3)**

H-D-Tyr-O-me hydrochloride 2.1 (25 g, 107.7 mmol) is dissolved in methylene chloride (150 mL) and aqueous sodium bicarbonate (22 g in 150 mL water), and then cooled to 0°C. To this resulting solution benzyl chloroformate (20 g, 118 mmol) is slowly added. After complete addition, the resulting solution is warmed to room temperature, and is then stirred for 2 h. The organic phase is separated, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure, to give the crude carbamate 2.2 (35g). The crude CBZ-Tyr-OMe product is

dissolved in methylene chloride (300 mL) containing concentrated H<sub>2</sub>SO<sub>4</sub>. Isobutene is bubbled through the solution for 6 h. The reaction is then cooled to 0°C, and neutralized with saturated NaHCO<sub>3</sub> aqueous solution. The organic phase is separated, dried, concentrated under reduced pressure, and purified by silica gel column chromatography to afford the tert-butyl ether 2.3 (25.7 g, 62 %).

**[2-(4-tert-Butoxy-phenyl)-1-formyl-ethyl]-carbamic acid benzyl ester (2.4)**

(Reference J. O. C. 1997, 62, 3884).

To a stirred -78°C methylene chloride solution (60 mL) of 2.3, DIBAL (82 mL of 1.5 M in toluene, 123 mmol) was added over 15 min. The resultant solution was stirred at -78°C for 30 min. Subsequently, a solution of EtOH/36 % HCl (9/1; 15 mL) is added slowly. The solution is added to a vigorously stirred aqueous HCl solution (600 mL, 1N) at 0°C. The layers are then separated, and the aqueous phase is extracted with cold methylene chloride. The combined organic phases are washed with cold 1N HCl aqueous solution, water, dried over Na<sub>2</sub>SO<sub>4</sub>, and then concentrated under reduced pressure to give the crude aldehyde 2.4 (20 g, 91 %).

**[4-Benzyloxycarbonylamino-1-(4-tert-butoxy-benzyl)-5-(4-tert-butoxy-phenyl)-2,3-dihydroxy-pentyl]-carbamic acid benzyl ester (2.5)**

To a slurry of VCl<sub>3</sub>(THF)<sub>3</sub> in methylene chloride (150 mL) at room temperature is added Zinc powder (2.9 g, 44 mmol), and the resulting solution is then stirred at room temperature for 1 hour. A solution of aldehyde 2.4 (20 g, 56 mmol) in methylene chloride (100 mL) is then added over 10 min. The resulting solution is then stirred at room temperature overnight, poured into an ice-cold H<sub>2</sub>SO<sub>4</sub> aqueous solution (8 mL in 200 mL), and stirred at 0°C for 30 min. The methylene chloride solution is separated, washed with 1N HCl until the washing solution is light blue. The organic solution is then concentrated under reduced pressure (solids are formed during concentration), and diluted with hexane. The precipitate is collected and washed thoroughly with a hexane/methylene chloride mixture to give the diol product 2.5. The filtrate is concentrated under reduced pressure and subjected to silica gel chromatography to afford a further 1.5 g of 2.5. (Total = 13 g, 65 %).

**[1-{5-[1-Benzyloxycarbonylamino-2-(4-tert-butoxy-phenyl)-ethyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-2-(4-tert-butoxy-phenyl)-ethyl]-carbamic acid benzyl ester (2.6)**

Diol 2.5 (5 g, 7 mmol) is dissolved in acetone (120 mL), 2,2-dimethoxypropane (20 mL), and pyridinium p-toluenesulfonate (120 mg, 0.5 mmol). The resulting solution is refluxed for 30 min., and then concentrated under reduced pressure to almost dryness. The resulting mixture is partitioned between methylene chloride and saturated NaHCO<sub>3</sub> aqueous solution, dried, concentrated under reduced pressure, and purified by silica gel column chromatography to afford isopropylidene protected diol 2.6 (4.8 g, 92 %).

**4,8-Bis-(4-tert-butoxy-benzyl)-2,2-dimethyl-hexahydro-1,3-dioxo-5,7-diaza-azulen-6-one(2.8)**

The diol 2.6 is dissolved in EtOAc/EtOH (10 mL/2 mL) in the presence of 10 % Pd/C and hydrogenated at atmospheric pressure to afford the diamino compound 2.7. To a solution of crude 2.7 in 1,1,2,2-tetrachloroethane is added 1,1-carboxydiimidazole (1.05 g, 6.5 mmol) at room temperature. The mixture is stirred for 10 min, and the resulting solution is then added dropwise to a refluxing 1,1',2,2'-tetrachloroethane solution (150 mL). After 30 min., the reaction mixture is cooled to room temperature, and washed with 5 % citric acid aqueous solution, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure, and purified by silica gel column chromatography to afford the cyclourea derivative 2.8 (1.92 g, 60 % over 2 steps).

**5,6-Dihydroxy-4,7-bis-(4-hydroxy-benzyl)-[1,3]diazepan-2-one (2.9)**

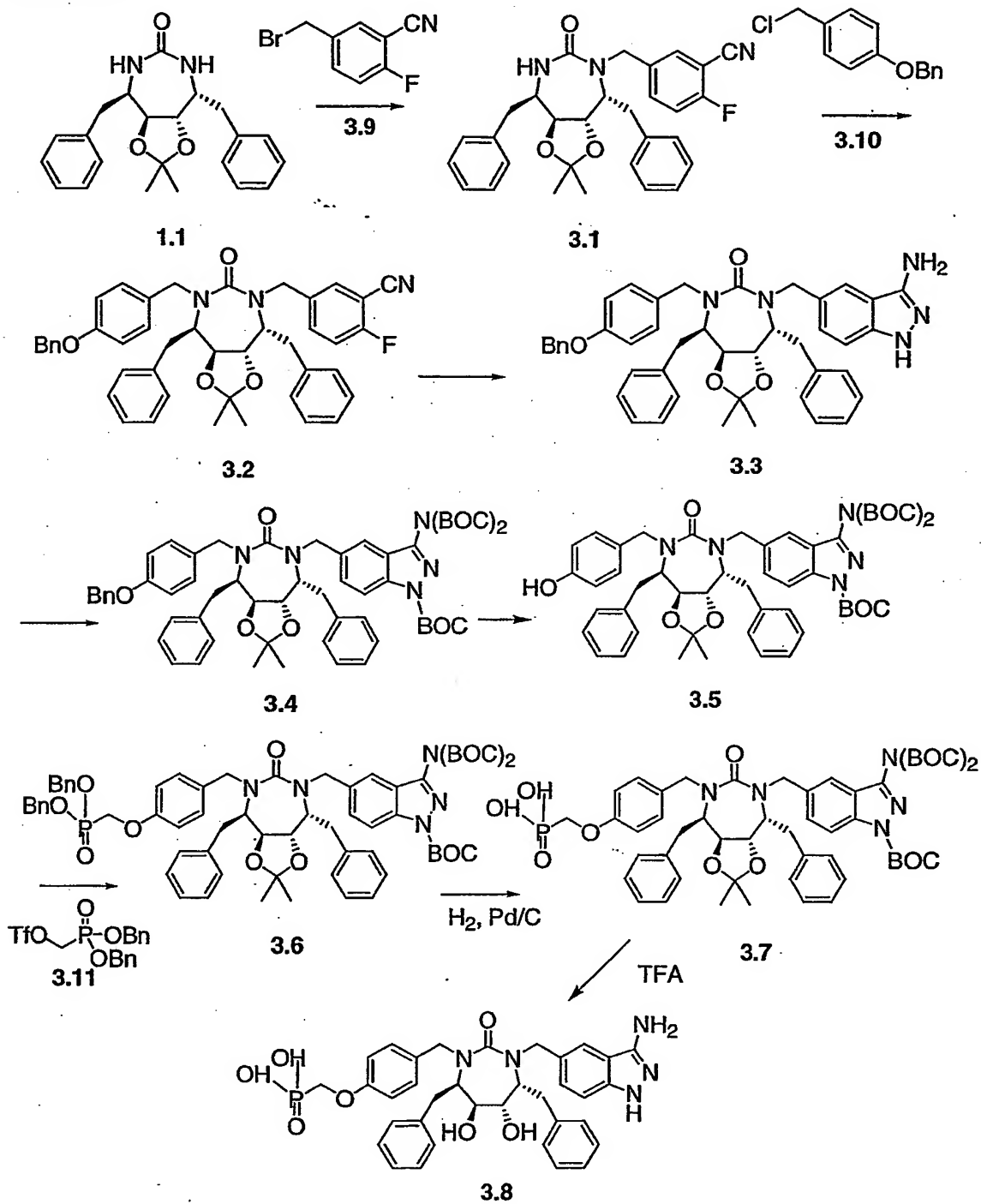
Cyclic Urea 2.8 (0.4 g, 0.78 mmol) was dissolved in dichloromethane (3 mL) and treated with TFA (1 mL). The mixture was stirred at room temperature for 2 h upon which time a white solid precipitated. 2 drops of water and methanol (2 mL) were added and the homogeneous solution was stirred for 1 h and concentrated under reduced pressure. The crude solid, 2.9, was dried overnight and then used without further purification.

**4,8-Bis-(4-hydroxy-benzyl)-2,2-dimethyl-hexahydro-1,3-dioxo-5,7-diaza-azulen-6-one (2.10)**

Diol 2.9 (1.8 g, 5.03 mmol) was dissolved in DMF (6 mL) and 2,2-dimethoxypropane (12 mL). P-TsOH (95 mg) was added and the mixture stirred at 65°C for 3 h. A vacuum was applied to remove water and then the mixture was stirred at 65°C for a further 1 h. The excess dimethoxypropane was then distilled and the remaining DMF solution was then

allowed to cool. The solution of acetonide **2.10** can then be used without further purification in future reactions.

Scheme 3



**3-Cyano-4-fluorobenzyl urea 3.1** : A solution of urea 1.1 (1.6 g, 4.3 mmol) in THF was treated with sodium hydride (0.5 g of 60 % oil dispersion, 13 mmol). The mixture was stirred at room temperature for 30 min and then treated with 3-cyano-4-fluorobenzyl bromide 3.9 (1.0 g, 4.8 mmol). The resultant solution was stirred at room temperature for 3 h, concentrated under reduced pressure, and then partitioned between  $\text{CH}_2\text{Cl}_2$  and saturated brine solution containing 1 % citric acid. The organic phase was separated, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel eluting with 15-25% ethyl acetate in hexanes to yield urea 3.1 (1.5 g, 69 %) as a white form.

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**Benzyl ether 3.2** : A solution of 3.1 (0.56 g, 1.1 mmol) in DMF (5 mL) was treated with sodium hydride (90 mg of 60 % oil dispersion, 2.2 mmol) and the resultant mixture stirred at room temperature for 30 min. 4-Benzyloxy benzyl chloride 3.10 (0.31 g, 1.3 mmol) was added and the resultant solution stirred at room temperature for 3 h. The mixture was concentrated under reduced pressure and then partitioned between  $\text{CH}_2\text{Cl}_2$  and saturated brine solution. The organic phase was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel eluting with 1-10% ethyl acetate in hexanes to yield compound 3.2 (0.52 g, 67 %) as white form.

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**Indazole 3.3**: Benzyl ether 3.2 (0.51 g, 0.73 mmol) was dissolved in n-butanol (10 mL) and treated with hydrazine hydrate (1 g, 20 mmol). The mixture was refluxed for 4 h and then allowed to cool to room temperature. The mixture was concentrated under reduced pressure and the residue was then partitioned between  $\text{CH}_2\text{Cl}_2$  and 10 % citric acid solution. The organic phase was separated, concentrated under reduced pressure, and then purified by silica gel column eluting with 5% methanol in  $\text{CH}_2\text{Cl}_2$  to afford indazole 3.3 (0.42 g, 82 %) as white solid.

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**Boc-indazole 3.4** : A solution of indazole 3.3 (0.4 g, 0.59 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) was treated with diisopropylethylamine (0.19 g, 1.5 mmol), DMAP (0.18 g, 1.4 mmol), and di-tert-butyl dicarbonate (0.4 g, 2 mmol). The mixture was stirred at room temperature for 3 h and then partitioned between  $\text{CH}_2\text{Cl}_2$  and 5 % citric acid solution. The organic phase was separated, dried over sodium sulfate, filtered and concentrated under reduced pressure. The

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residue was purified by silica gel eluting with 2% methanol in  $\text{CH}_2\text{Cl}_2$  to afford 3.4 (0.42 g, 71 %).

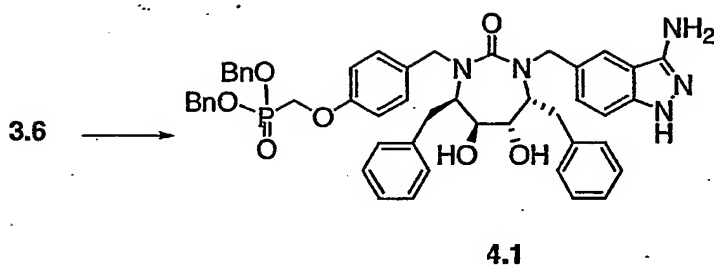
**Phenol 3.5 :** A solution of 3.4 (300 mg, 0.3 mmol) in ethyl acetate (10 mL) and methanol (10 mL) was treated with 10 % Pd/C (40 mg) and stirred under a hydrogen atmosphere (balloon) for 16 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to yield 3.5 as a white powder. This was used without further purification.

**Dibenzyl ester 3.6 :** A solution of 3.5 (0.1 mmol) in THF (5 mL) was treated with dibenzyl triflate 3.11 (90 mg, 0.2 mmol), and cesium carbonate (0.19 g, 0.3 mmol). The mixture was stirred at room temperature for 4 h and then concentrated under reduced pressure. The residue was partitioned between  $\text{CH}_2\text{Cl}_2$  and saturated brine. The organic phase was separated, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel eluting with 20-40% ethyl acetate in hexanes to afford 3.6 (70 mg, 59 %).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.07 (d, 1H), 7.20-7.43 (m, 16H), 7.02-7.15 (m, 8 H), 6.80 (d, 2H), 5.07-5.18 (m, 4H), 5.03 (d, 1H), 4.90 (d, 1H), 4.20 (d, 2H), 3.74-3.78 (m, 4H), 3.20 (d, 1H), 3.05 (d, 1H) 2.80-2.97 (m, 4H), 1.79 (s, 9H), 1.40 (s, 18H), 1.26 (s, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ ): 20.5 ppm.

**Phosphonic acid 3.7:** A solution of dibenzylphosphonate 3.6 (30 mg) in EtOAc (10 mL) was treated with 10% Pd/C (10 mg) and the mixture was stirred under a hydrogen atmosphere (balloon) for 3 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to afford phosphonic acid 3.7. This was used without further purification.

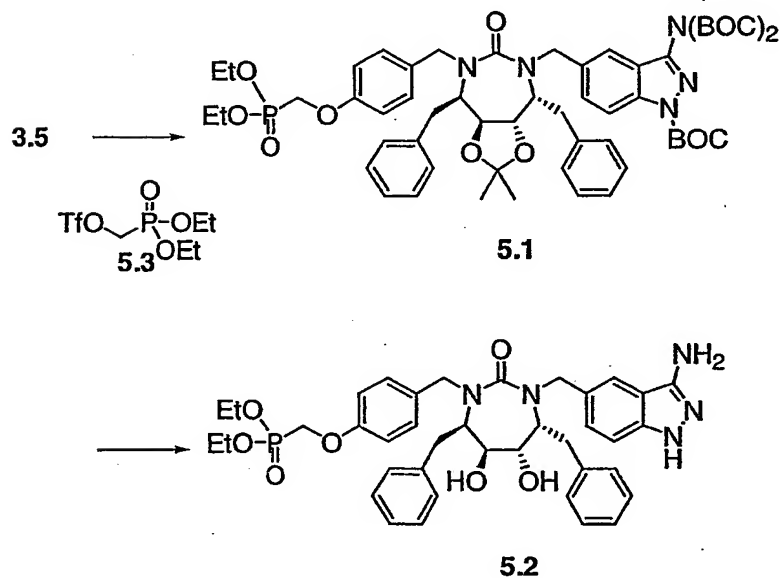
**Phosphonic acid 3.8:** The crude phosphonic acid 3.7 was dissolved in  $\text{CH}_2\text{Cl}_2$  (2 mL) and treated with trifluoroacetic acid (0.4 mL). The resultant mixture was stirred at room temperature for 4 h. The mixture was concentrated under reduced pressure and then purified by preparative HPLC (35 %  $\text{CH}_3\text{CN}$ /65 %  $\text{H}_2\text{O}$ ) to afford the phosphonic acid 3.8 (9.4 mg, 55 %).  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  7.71 (s, 1H), 7.60 (d, 1H), 6.95-7.40 (m, 15H), 4.65 (d, 2H), 4.17 (d, 2H), 3.50-3.70 (m, 3H), 3.42 (d, 1H), 2.03-3.14 (m, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ ): 17.30

## Scheme 4



**Dibenzylphosphonate 4.1:** A solution of **3.6** (30 mg, 25  $\mu$ mol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) was  
 5 treated with TFA (0.4 mL) and the resultant mixture was stirred at room temperature for 4 h.  
 The mixture was concentrated under reduced pressure and the residue was purified by silica  
 gel eluting with 50% ethyl acetate in hexanes to afford **4.1** (5 mg, 24%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$   
 6.96-7.32 (m, 25H), 6.95 (d, 2H), 5.07-5.18 (m, 4H), 4.86 (d, 1H), 4.75 (d, 1H), 4.18 (d, 2H),  
 3.40-3.62 (m, 4H), 3.25 (d, 1H), 2.80-3.15 (m, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ ) 20.5 ppm; MS : 852  
 10 (M + H), 874 (M + Na).

## Scheme 5



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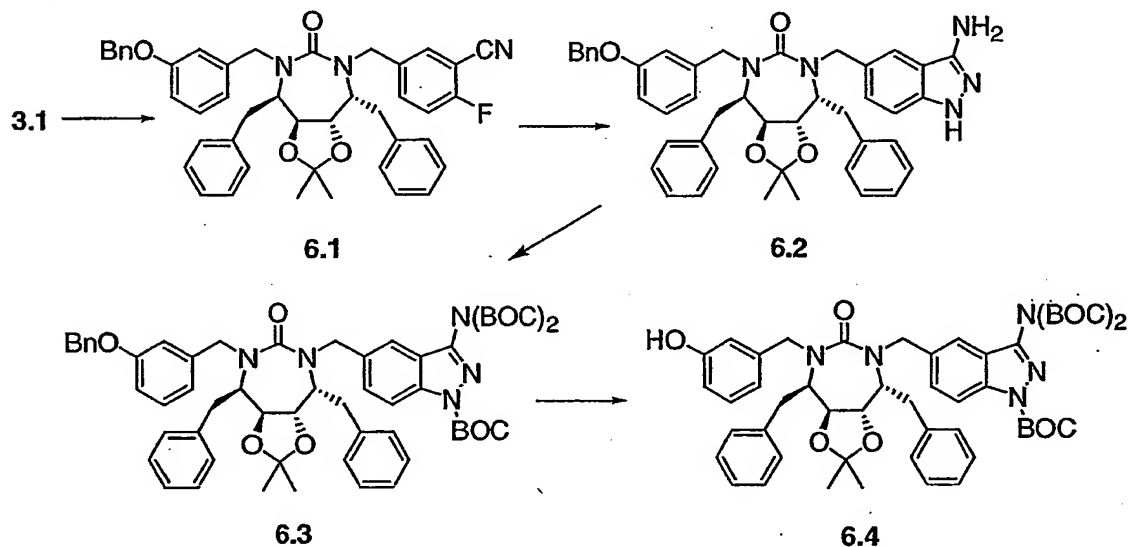
**Diethylphosphonate 5.1:** A solution of phenol **3.5** (48 mg, 52  $\mu$ mol) in THF (5 mL) was  
 treated with triflate **5.3** (50 mg, 165  $\mu$ mol), and cesium carbonate (22 mg, 0.2 mmol). The

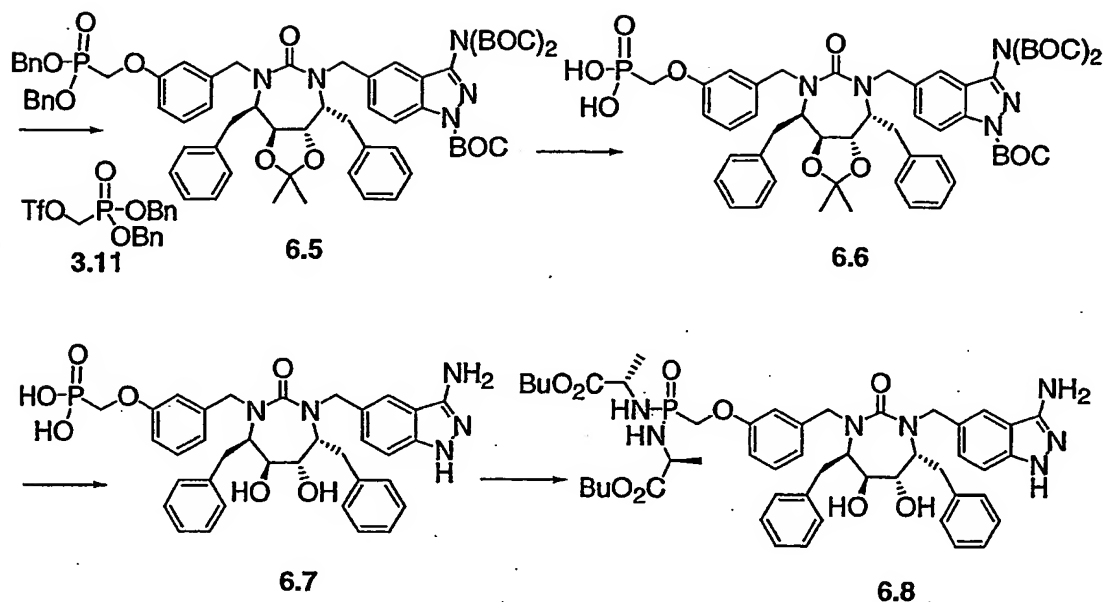


resultant mixture was stirred at room temperature for 5 h and then concentrated under reduced pressure. The residue was partitioned between  $\text{CH}_2\text{Cl}_2$  and saturated brine. The organic phase was separated, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel eluting with 7% methanol in  $\text{CH}_2\text{Cl}_2$  to afford **5.1** (28 mg, 50 %).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.06 (d, 1H), 7.30-7.43 (m, 7H), 7.02-7.30 (m, 7H), 6.88 (d, 2H), 5.03 (d, 1H), 4.90 (d, 1H), 4.10-4.25 (m, 6H), 3.64-3.80 (m, 4H), 3.20 (d, 1H), 3.05 (d, 1H), 2.80-2.97 (m, 4H), 1.79 (s, 9H), 1.20-1.50 (m, 30H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ ): 18.5 ppm; MS :1068 (M + H), 1090 (M + Na).

- 10 **Diethylphosphonate 5.2:** A solution of **5.1** (28 mg, 26  $\mu\text{mol}$ ) in  $\text{CH}_2\text{Cl}_2$  (2 mL) was treated with TFA (0.4 mL) and the resultant mixture was stirred at room temperature for 4 hrs. The mixture was concentrated under reduced pressure and the residue was purified by silica gel to afford **5.2** (11 mg, 55 %).  $^1\text{H}$  NMR ( $\text{CDCl}_3 + 10\% \text{CD}_3\text{OD}$ ):  $\delta$  6.96-7.35 (m, 15H), 6.82 (d, 2H), 4.86(d, 1H), 4.75 (d, 1H), 4.10-4.23 (M, 6H), 3.40-3.62 (m, 4H), 2.80-3.20 (m), 1.31 (t, 6 H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3 + 10\% \text{CD}_3\text{OD}$ ): 19.80 ppm; MS : 728 (M + H).

Scheme 6





**3-Benzyloxybenzyl urea 6.1** : The urea 3.1 (0.87 g, 1.7 mmol) was dissolved in DMF and treated with sodium hydride (60% dispersion, 239 mg, 6.0 mmol) followed by m-benzyloxybenzylbromide 6.9 (0.60 g, 2.15 mmol). The mixture was stirred for 5 h and then diluted with ethyl acetate. The solution was washed with water, brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel eluting with 25% ethyl acetate in hexanes to afford urea 6.1 (0.9 g, 75%).

**Indazole 6.2**: The urea 6.1 (41 mg, 59  $\mu$ mol) was dissolved in n-butanol (1.5 mL) and treated with hydrazine hydrate (100  $\mu$ L, 100 mmol). The mixture was refluxed for 2 h and then allowed to cool. The mixture was diluted with ethyl acetate, washed with 10% citric acid solution, brine, saturated  $\text{NaHCO}_3$ , and finally brine again. The organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure to give the crude product 6.2 (35 mg, 83%). (Chem. Biol. 1998, 5, 597-608).

**Boc-indazole 6.3** : The indazole 6.2 (1.04 g, 1.47 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (20 mL) and treated with di-*t*-butyl dicarbonate (1.28 g, 5.9 mmol), DMAP (0.18 g, 1.9 mmol) and DIPEA (1.02 mL, 9.9 mmol). The mixture was stirred for 3 h and then diluted with ethyl acetate. The solution was washed with 5% citric acid solution,  $\text{NaHCO}_3$ , brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel eluting with 50% ethyl acetate in hexanes to give 6.3 (0.71 g, 49%).

**Phenol 6.4 :** Compound 6.3 (20 mg, 0.021 mmol) was dissolved in MeOH (1 mL) and EtOAc (1 mL) and treated with 10% Pd/ C catalyst (5 mg). The mixture was stirred under a hydrogen atmosphere (balloon) until completion. The catalyst was removed by filtration and  
5 the filtrate concentrated under reduced pressure to afford compound 6.4 (19 mg, 100%).

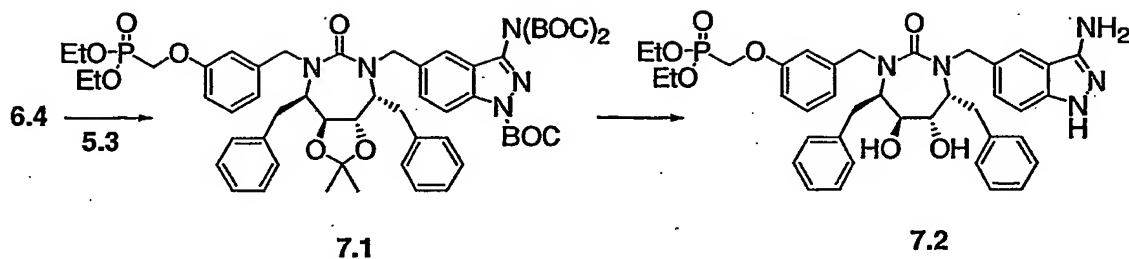
**Dibenzyl phosphonate 6.5:** A solution of compound 6.4 (0.34 g, 0.37 mmol) in acetonitrile (5 mL) was treated with  $\text{Cs}_2\text{CO}_3$  (0.36 g, 1.1 mmol) and triflate 3.11 (0.18 mL, 0.52 mmol). The reaction mixture was stirred for 1 h. The reaction mixture was filtered and the filtrate  
10 was then concentrated under reduced pressure. The residue was re-dissolved in EtOAc, washed with water, saturated  $\text{NaHCO}_3$ , and finally brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by silica gel eluting with hexane: EtOAc (1:1) to afford compound 6.5 (0.32 g, 73%).

**Phosphonic acid 6.6:** Compound 6.5 (208 mg, 0.174 mmol) was treated in the same manner as benzyl phosphonate 3.6 in the preparation of phosphonate diacid 3.7, except MeOH was used as the solvent, to afford compound 6.6 (166 mg, 94%).

**Phosphonic acid 6.7:** Compound 6.6 (89 mg, 0.088 mmol) was treated according to the  
20 conditions described in Scheme 3 for the conversion of 3.7 into 3.8. The residue was purified by preparative HPLC eluting with a gradient of 90% methanol in 100 mM TEA bicarbonate buffer and 100% TEA bicarbonate buffer to afford phosphonic acid 6.7 (16 mg, 27%)

**Bisamidate 6.8 :** Triphenylphosphine (112 mg, 0.43 mmol) and aldrithiol-2 (95 mg, 0.43  
25 mmol) were mixed in dry pyridine (0.5 mL). In an adjacent flask the diacid 6.7 (48 mg, 0.71 mmol) was suspended in dry pyridine (0.5 mL) and treated with DIPEA (0.075 mL 0.43 mmol) and L-AlaButyl ester hydrochloride (78 mg, 0.43 mmol) and finally the triphenylphosphine, aldrithiol-2 mixture. The reaction mixture was stirred under nitrogen for 24 h then concentrated under reduced pressure. The residue was purified by preparative  
30 HPLC eluting with a gradient of 5% to 95% acetonitrile in water. The product obtained was then further purified by silica gel eluting with  $\text{CH}_2\text{Cl}_2$  : MeOH (9:1) to give compound 6.8 (9 mg, 14%).

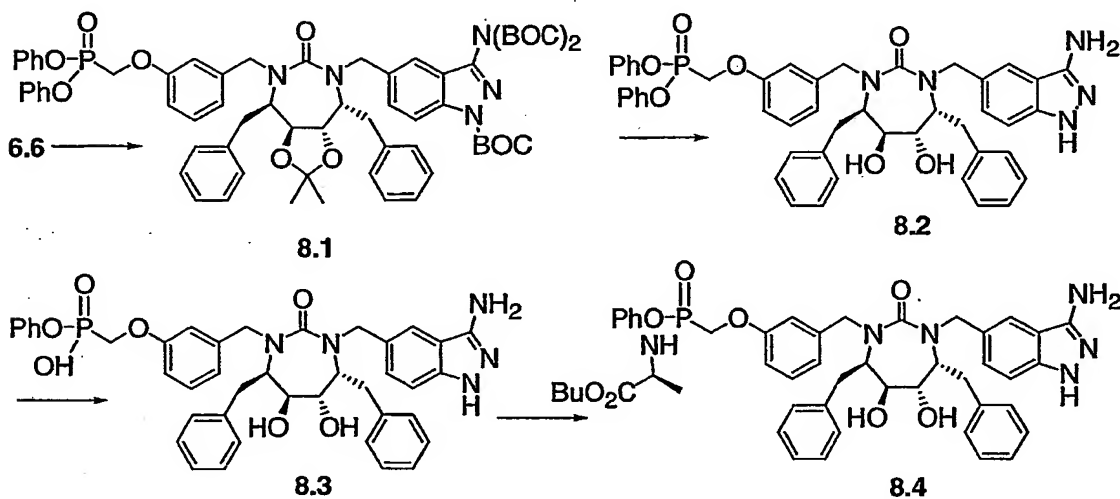
## Scheme 7



- 5 **Diethyl phosphonate 7.1** : Compound 6.4 (164 mg, 0.179 mmol) was treated according to the procedure used to generate compound 6.5 except triflate 5.3 was used in place of triflate 3.11 to afford compound 7.1 (142 mg, 74%).

- 10 **Diethylphosphonate 7.2** : Compound 7.1 (57 mg, 0.053 mmol) was treated according to the conditions used to form 6.7 from 6.6. The residue formed was purified by silica gel eluting with  $\text{CH}_2\text{Cl}_2$  : MeOH (9:1) to afford compound 7.2 (13 mg, 33%).

## Scheme 8



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- Diphenylphosphonate 8.1**: A solution of 6.6 (0.67g, 0.66 mmol) in pyridine (10 mL) was treated with phenol (0.62 g, 6.6 mmol) and DCC (0.82 mg, 3.9 mmol). The resultant mixture was stirred at room temperature for 5 min and then the solution was heated at 70°C for 3 h.
- 20 The mixture was allowed to cool to room temperature and then diluted with EtOAc and water

(2 mL). The resultant mixture was stirred at room temperature for 30 min and then concentrated under reduced pressure. The residue was triturated with  $\text{CH}_2\text{Cl}_2$ , and the white solid that formed was removed by filtration. The filtrate was concentrated under reduced pressure and the resultant residue was purified by silica gel eluting with 30% ethyl acetate in hexanes to yield **8.1** (0.5 g, 65 %).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.08 (d, 1H), 7.41 (d, 1H), 7.05-7.35 (m, 22H), 6.85 (d, 2H), 6.70 (s, 1H), 5.19 (d, 1H), 5.10 (d, 1H), 4.70 (d, 2H), 3.70-3.90 (m, 4H), 3.20 (d, 1H), 3.11 (d, 1H), 2.80-2.97 (m, 4H), 1.79 (s, 9H), 1.40 (s, 18H), 1.30 (s, 6H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ ): 12.43 ppm

**Diphenylphosphonate 8.2** : A solution of **8.1** (0.5 g, 0.42 mmol) in  $\text{CH}_2\text{Cl}_2$  (4 mL) was treated with TFA (1 mL) and the resultant mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure and azeotroped twice with  $\text{CH}_3\text{CN}$ . The residue was purified by silica gel eluting with 5% methanol in  $\text{CH}_2\text{Cl}_2$  to afford diphenylphosphonate **8.2** (0.25 g, 71 %).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.03-7.40 (m, 21H), 6.81-6.90 (m, 3H), 4.96 (d, 1H), 4.90 (d, 1H), 4.60-4.70 (m, 2H), 3.43-3.57 (m, 4H), 3.20 (d, 1H), 2.80-2.97 (m, 5H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ ): 12.13 ppm; MS : 824 (M + H).

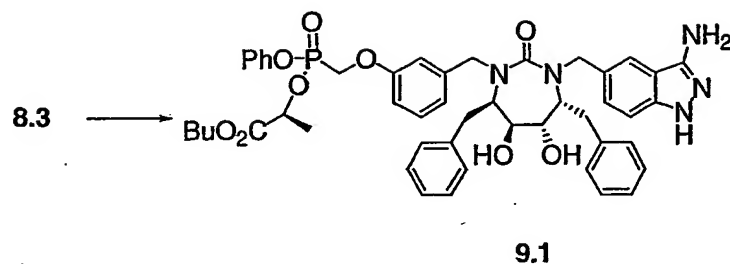
**Monophenol 8.3** : The monophenol **8.3** (124 mg, 68 %) was prepared from the diphenol **8.2** by treating with 1N NaOH in acetonitrile at 0°C.

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**Monoamidate 8.4** : To a pyridine solution (0.5 mL) of **8.3** (40 mg, 53  $\mu\text{mol}$ ), n-butyl amidate HCl salt (116 mg, 640  $\mu\text{mol}$ ), and DIPEA (83 mg, 640  $\mu\text{mol}$ ) was added a pyridine solution (0.5 mL) of triphenyl phosphine (140 mg, 640  $\mu\text{mol}$ ), and aldrithiol-2 (120 mg, 640  $\mu\text{mol}$ ). The resulting solution was stirred at 65°C overnight, worked up, and purified by preparative TLC twice to give **8.4** (1.8 mg).  $\delta$  4.96 (d, 1H), 4.90 (d, 1H), 4.30-4.6 (m, 2H), 3.9-4.2 (m, 2H), 3.6-3.70 (m, 4H), 3.2-3.3 (d, 1H), 2.80-3.1 (m, 4H); MS: 875 (M + H) & 897 (M + Na)

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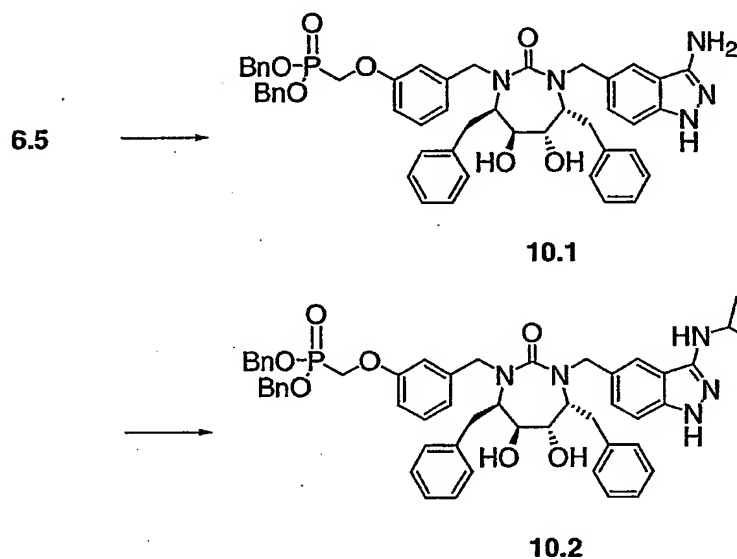
## Scheme 9



- 5 Monolactate **9.1**: The monolactate **9.1** is prepared from **8.3** using the conditions described above for the preparation of the monoamidate **8.4** except n-butyl lactate was used in place of n-butyl amidate HCl salt.

## Scheme 10

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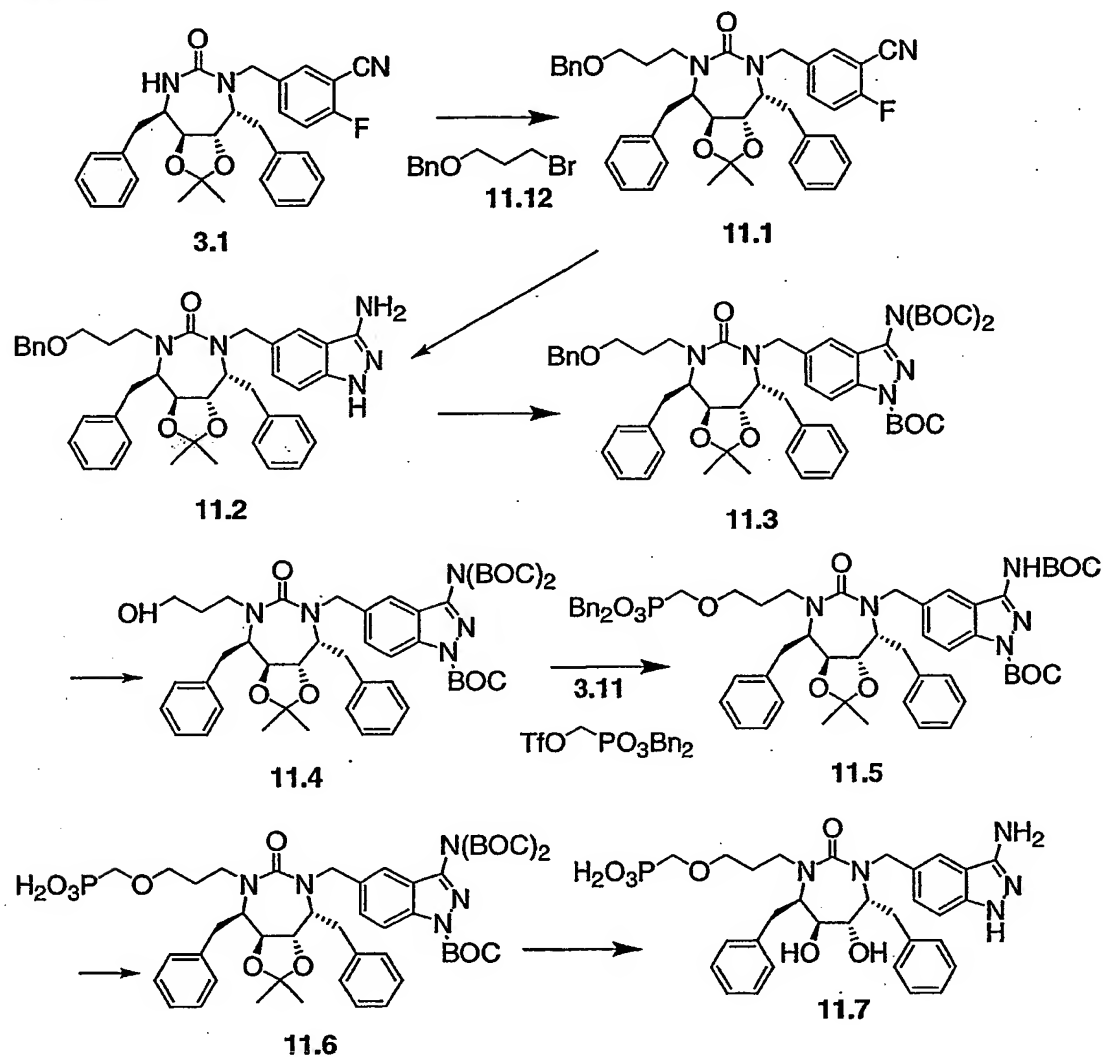


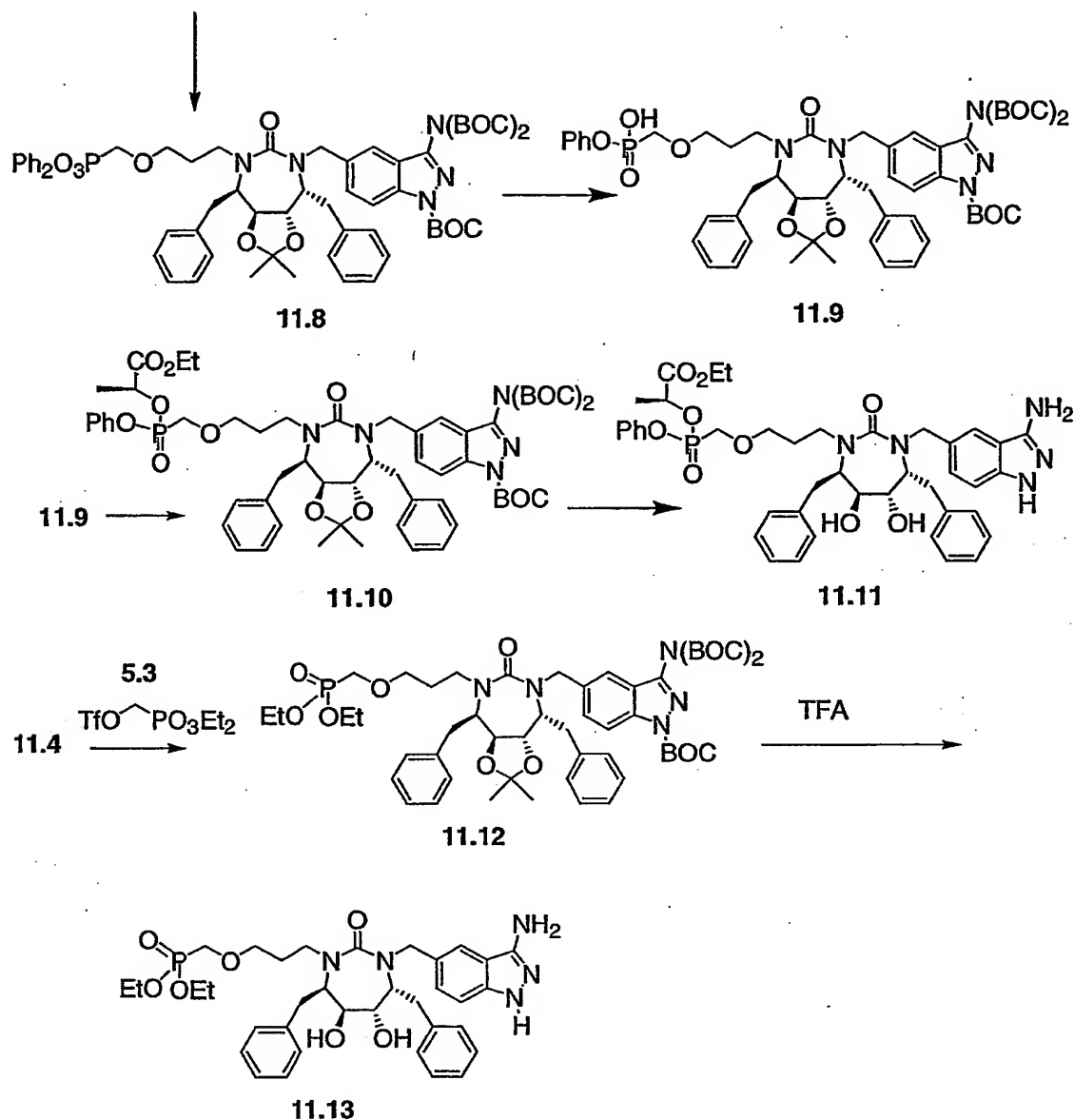
- Dibenzylphosphonate 10.1**: Compound **6.5** (16 mg, 0.014 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (2 mL) and cooled to  $0^\circ\text{C}$ . TFA (1 mL) was added and the reaction mixture was stirred for 0.5 h. The mixture was then allowed to warm to room temperature for 2 h. The reaction mixture was concentrated under reduced pressure and azeotroped with toluene. The residue was purified by silica gel eluting with  $\text{CH}_2\text{Cl}_2$  : MeOH (9:1) to afford compound **10.1** (4 mg, 32%).

**Isopropylamino indazole 10.2 :** Compound 10.1 (30 mg, 0.35 mmol) was treated with acetone according to the method of Henke et al. (J. Med Chem. 40 17 (1997) 2706-2725) to yield 10.2 as a crude residue. The residue was purified by silica gel eluting with CH<sub>2</sub>Cl<sub>2</sub> : MeOH (93:7) to afford compound 10.2 (3.4 mg, 10%).

5

### Scheme 11





**Benzyl ether 11.1:** A DMF solution (5 mL) of 3.1 (0.98 g, 1.96 mmol) was treated with NaH (0.24 g of 60 % oil dispersion, 6 mmol) for 30 min, followed by the addition of sodium iodide (0.3 g, 2 mmol), and benzyloxypropyl bromide (0.55 g, 2.4 mmol). After the reaction for 3 h at room temperature, the reaction mixture was partitioned between methylene chloride and saturated NaCl, dried, and purified to give 11.1 (0.62 g, 49 %).

**Aminoindazole 11.2:** A n-butanol solution (10 mL) of 11.1 (0.6 g, 0.92 mmol) and hydrazine hydrate (0.93 g, 15.5 mmol) was heated at reflux for 4 h. The reaction mixture was concentrated under reduced pressure to give crude 11.2 (~0.6 g).



**Tri-BOC-Aminoindazole 11.3:** A methylene chloride solution (10 mL) of crude **11.2**, DIPEA (0.36 g, 2.8 mmol), (BOC)<sub>2</sub>O (0.73 g, 3.3 mmol), and DMAP (0.34 g, 2.8 mmol) was stirred for 5 h at room temperature, partitioned between methylene chloride and 5 % citric acid solution, dried, purified by silica gel column chromatography to give **11.3** (0.51 g, 58 %, 2 steps).

**3-Hydroxypropyl cyclic urea 11.4:** An ethyl acetate/ethanol solution (30 mL/5 mL) of **11.3** (0.5 g, 0.52 mmol) was hydrogenated at 1 atm in the presence of 10 % Pd/C (0.2 g) for 4 h. The catalyst was removed by filtration. The filtrate was then concentrated under reduced pressure to afford crude **11.4** (0.44 g, 98 %).

**Dibenzyl phosphonate 11.5:** A THF solution (3 mL) of **11.4** (0.5 g, 0.57 mmol) and triflate dibenzyl phosphonate **3.11** (0.37 g, 0.86 mmol) was cooled to -3°C, followed by addition of n-BuLi (0.7 mL of 2.5 M hexane solution, 1.7 mmol). After 2 h reaction, the reaction mixture was partitioned between methylene chloride and saturated NaCl solution, concentrated under reduced pressure. The residue was redissolved in methylene chloride (10 mL), and reacted with (BOC)<sub>2</sub>O (0.15 g, 0.7 mmol) in the presence of DMAP (0.18 g, 0.57 mmol), DIPEA (0.18 g, 1.38 mmol) for 2 h at room temperature. The reaction mixture was worked up, and purified by silica gel chromatography to give **11.5** (0.25 g, 43 %).

**Phosphonic diacid 11.7:** An ethyl acetate solution (2 mL) of **11.5A** (11 mg, 10.5 µmol) was hydrogenated at 1 atm in the presence of 10% Pd/C (10 mg) for 6 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to give crude **11.6**. The crude **11.6** was redissolved in methylene chloride (1 mL) and treated with TFA (0.2 mL) for 4 h at room temperature. The reaction mixture was concentrated under reduced pressure and purified by HPLC to give **11.7** (2 mg, 30%).

NMR (CD<sub>3</sub>OD): δ 7.1-7.3 (m, 11H), 7.0-7.1 (d, 2H), 4.95 (d, 1H), 3.95-4.1 (d, 1H), 2.9-3.3 (m, 4H), 2.3-2.45 (m, 1H), 1.6-1.8 (m, 2H). P NMR (CD<sub>3</sub>OD): 15.5 ppm. MS: 624 (M + 1).

**Diphenyl phosphonate 11.8:** A pyridine solution (1 mL) of **11.6** (0.23 g, 0.23 mmol), phenol (0.27 g, 2.8 mmol), and DCC (0.3 g, 1.4 mmol) was stirred for 5 min. at room temperature, then reacted at 70°C for 3 h. The reaction mixture was cooled to room

temperature, concentrated under reduced pressure, and purified by silica gel column chromatograph to afford **11.8** (0.11g, 41 %).

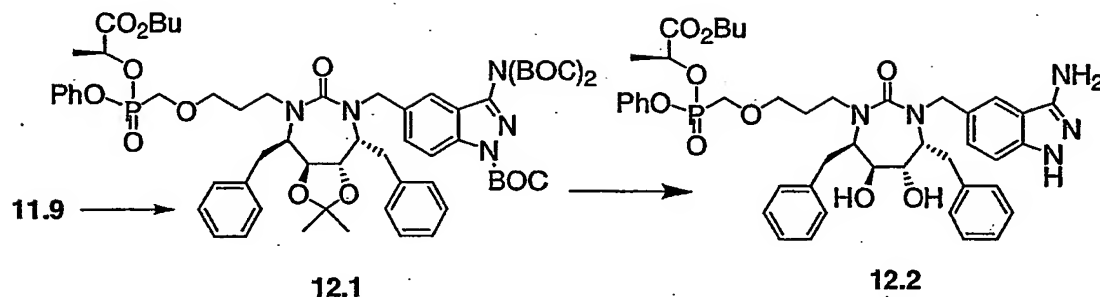
5 **Monophenyl phosphonate 11.9:** An acetonitrile solution (2 mL) of **11.8** (0.12 g, 0.107 mmol) at 0°C was treated with 1N sodium hydroxide aqueous solution (0.2 mL) for 1.5 h, then acidified with Dowex (50wx8-200, 120 mg). The Dowex was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was triturated with 10 % EtOAc/90 % hexane twice to afford **11.9** (90 mg, 76 %) as a white solid.

10 **Mono-ethyl lactate phosphonate 11.10:** A pyridine solution (0.3 mL) of **11.9** (33 mg, 30  $\mu$ mol), ethyl lactate (41 mg, 340  $\mu$ mol), and DCC (31 mg, 146  $\mu$ mol) was stirred at room temperature for 5 min, then reacted at 70°C for 1.5 h. The reaction mixture was concentrated under reduced pressure, partitioned between methylene chloride and saturated NaCl solution, and purified by silica gel chromatography to give **11.10** (18 mg, 50 %).

15 **Ethyl lactate phosphonate 11.11:** A methylene chloride solution (0.8 mL) of **11.10** (18 mg, 15.8  $\mu$ mol) was treated with TFA (0.2 mL) for 4 h, and then concentrated under reduced pressure. The residue was purified by preparative TLC to give **11.11** (6 mg, 50 %). NMR (CDCl<sub>3</sub> + ~10 %CD<sub>3</sub>OD):  $\delta$  7.0-7.3 (m, 16 H), 6.8-7.0 (m, 2H), 4.9-5.0 (m, 1H), 4.75 (d, 1H), 4.1-4.2 (m, 2H), 3.5-4.0 (m, 10H), 2.18-2.3. (m, 1H), 1.6-1.7 (m, 1), 1.47 & 1.41 (2d, 20 3H), 1.22 (t, 3H). P NMR (CDCl<sub>3</sub> + ~10 %CD<sub>3</sub>OD): 19.72 & 17.86 ppm.

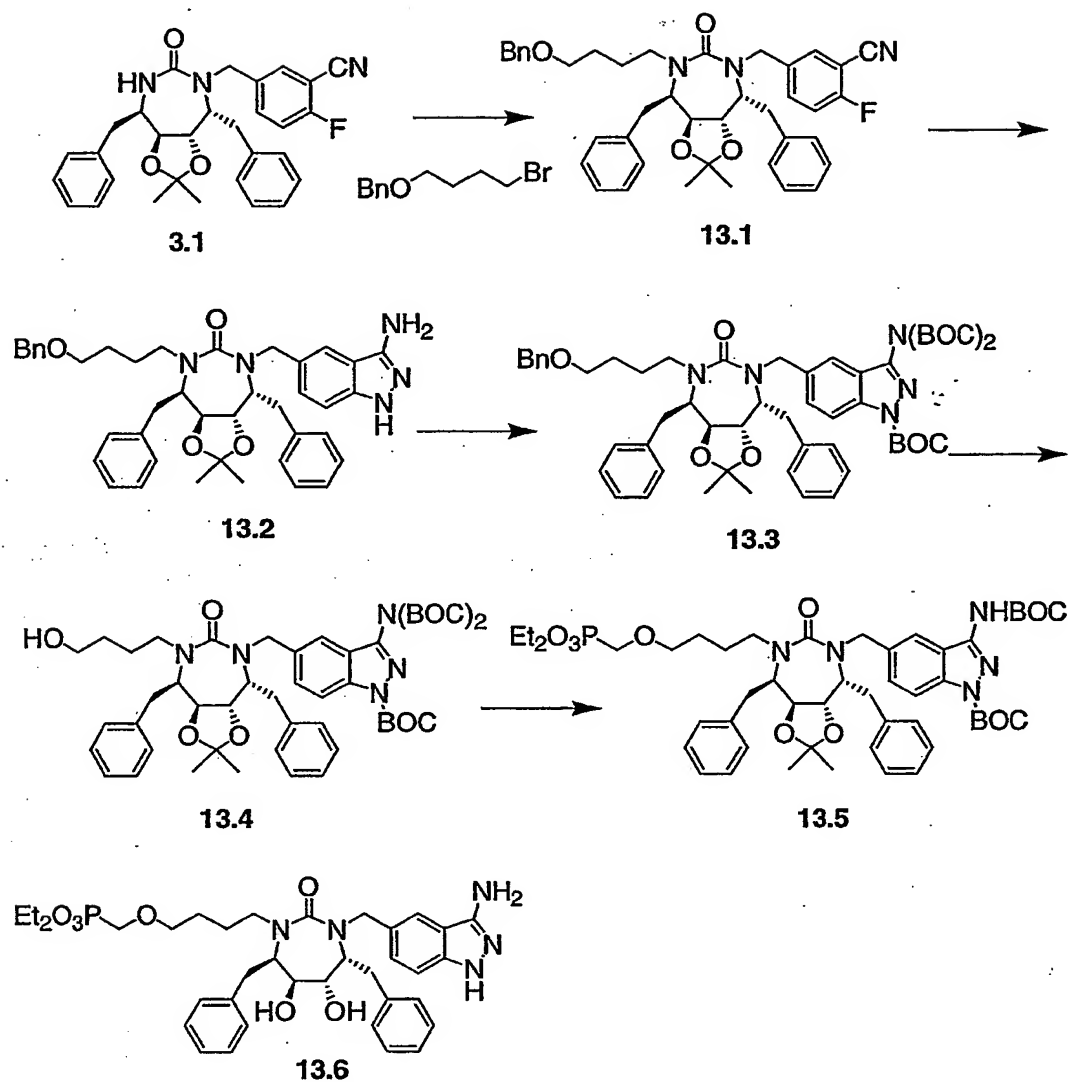
**Diethyl phosphonate 11.13:** Compound **11.13** (6 mg) was prepared as described above in Scheme 5 from **11.4** (30 mg, 34  $\mu$ mol) and triflate phosphonate **5.3** (52 mg, 172  $\mu$ mol), 25 followed by TFA treatment. NMR (CDCl<sub>3</sub> + ~10 %CD<sub>3</sub>OD):  $\delta$  7.1-7.32 (m, 11 H), 6.9-7.0 (d, 2H), 4.75 (d, 1H), 4.1-4.2 (2q, 4H), 3.84-3.9 (m, 1H), 3.4-3.8 (m, 8H), 2.7-3.1 (m, 4H), 2.1-2.5 (m, 1H), 1.5-1.7 (m, 2H), 1.25-1.35 (2t, 6H). P NMR (CDCl<sub>3</sub> + ~10 %CD<sub>3</sub>OD): 21.63 ppm. MS: 680 (M + 1).

Scheme 12



- 5 **Butyl lactate phosphonate 12.2:** A pyridine solution (0.3 mL) of **11.9** (27 mg, 22  $\mu$ mol), butyl lactate (31 mg, 265  $\mu$ mol), and DCC (28 mg, 132  $\mu$ mol) was stirred at room temperature for 5 min, then reacted at 70°C for 1.5 h. The reaction mixture was concentrated under reduced pressure, partitioned between methylene chloride and saturated NaCl solution, and purified by preparative TLC to give **12.1** (12 mg). A methylene chloride solution (0.8 mL) of **12.1** (12 mg) was treated with TFA (0.2 mL) for 4 h, concentrate. The residue was
- 10 purified by preparative TLC to give **12.2** (3 mg, 16 %). NMR ( $\text{CDCl}_3 + \sim 10\% \text{CD}_3\text{OD}$ ):  $\delta$  6.8-7.4 (m, 18H), 6.4-6.6 (m), 4.9-5.05 (m, 1H), 4.75 (d, 1H), 4.1-4.2 (m, 2H), 3.5-4.0 (m, 10H), 3.1-3.25 (m, 2H), 2.2-2.35 (m, 1H), 1.8-1.9 (m, 1H), 1.4 & 1.8 (m, 7H), 1.22 (t, 3H). P NMR ( $\text{CDCl}_3 + \sim 10\% \text{CD}_3\text{OD}$ ): 19.69 & 17.86 ppm.

Scheme 13



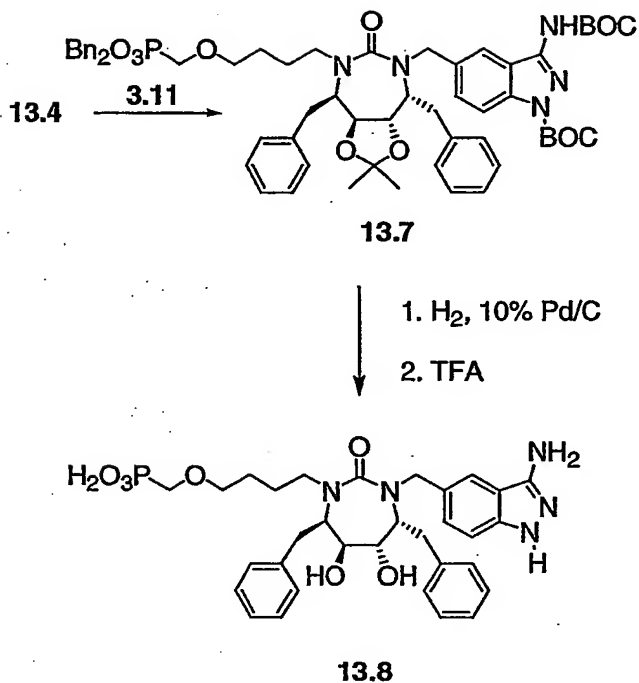
- Benzyl ether 13.1:** A DMF solution (5 mL) of 3.1 (1 g, 2 mmol) was treated with NaH (0.24 g of 60% oil dispersion, 6 mmol) for 30 min, followed by the addition of sodium iodide (0.3 g, 2 mmol), and benzoyloxybutyl bromide (0.58 g, 2.4 mmol). After the reaction for 5 h at room temperature, the reaction mixture was partitioned between methylene chloride and saturated NaCl, dried, and purified to give 13.1 (0.58 g, 44 %).
- Aminoindazole 13.2:** A n-butanol solution (10 mL) of 11.1 (0.58 g, 0.87 mmol) and hydrazine hydrate (0.88 g, 17.5 mmol) was heated at reflux for 4 h. The reaction mixture was concentrated under reduced pressure to give crude 13.2 (0.56 g).

**Tri-BOC-aminoindazole 13.3:** A methylene chloride solution (10 mL) of **13.2** (0.55 g, 0.82 mmol), DIPEA (0.42 g, 3.2 mmol), (BOC)<sub>2</sub>O (0.71 g, 3.2 mmol), and DMAP (0.3 g, 2.4 mmol) was stirred for 4 h at room temperature, partitioned between methylene chloride and 5% citric acid solution, dried, purified by silica gel chromatography to give **13.3** (0.56 g, 71 %, 2 steps).

**3-Hydroxybutyl cyclic urea 13.4:** An ethyl acetate/methanol solution (30 mL/5 mL) of **11.3** (0.55 g, 0.56 mmol) was hydrogenated at 1 atm in the presence of 10% Pd/C (0.2 g) for 3 h. The catalyst was removed by filtration. The filtrate was concentrated under reduced pressure to afford crude **13.4** (0.5 g, 98 %).

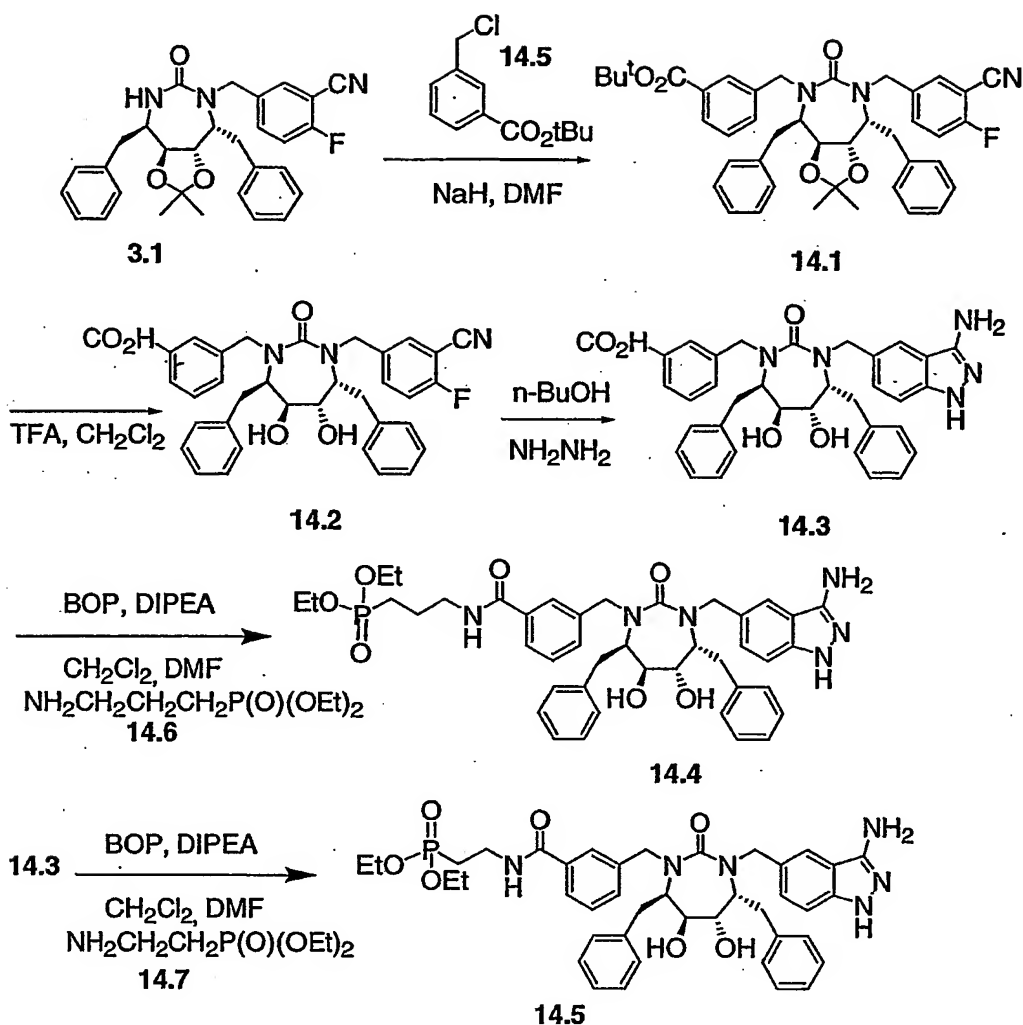
**Diethyl phosphonate 13.6:** A THF solution (1 mL) of **13.4** (5 mg, 56 µmol) and triflate diethyl phosphonate **5.3** (30 mg, 100 µmol) was cooled to -3°C, followed by addition of n-BuLi (80 µl of 2.5 M hexane solution, 200 µmol). After 2 h reaction, the reaction mixture was partitioned between methylene chloride and saturated NaCl solution, concentrated under reduced pressure to give crude **13.5**. The residue was dissolved in methylene chloride (0.8 mL) and treated with TFA (0.2 mL) for 4 h. concentrated under reduced pressure, and purified by HPLC to give **13.6** (8 mg, 21%). NMR (CDCl<sub>3</sub>): δ 7.1-7.4 (m, 11H), 7.0-7.1 (m, 2H) 4.81 (d, 1H), 4.1-4.25 (m, 4H). 3.85-3.95 (m, 1H), 3.4-3.8 (m, 7H), 3.3-3.4 (m, 1H), 2.8 - 3.25 (m, 5H), 2.0-2.15 (m, 1H), 1.3-1.85 (m, 10H). P NMR (CDCl<sub>3</sub>): 21.45 ppm.

Scheme 13a



- 5 **Phosphonic diacid 13.8:** Compound **13.8** (4.5 mg) was prepared from **13.4** as described above for the preparation of **11.7** from **11.4** (Scheme 11). NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  7.41 (s, 1H), 7.1-7.4 (m, 10H), 6.9-7.0 (m, 2H), 4.75 (d, 1H), 3.8-4.0 (m, 1H), 3.4-3.8 (m, 8H), 2.8-3.25 (m, 5H), 2.1-2.25 (m, 1H), 1.6-1.85 (m, 4H). MS: 638 ( $\text{M} + 1$ ).

Scheme 14



- 5 **t-Butyl ester 14.1:** A DMF solution (3 mL) of 3.1 (0.5 g, 1 mmol) was treated with NaH (80 mg of 60% oil dispersion, 2 mmol) for 10 min, followed by the addition of 14.5 (0.25 g, 1.1 mmol). After the reaction for 1 h at room temperature, the reaction mixture was partitioned between methylene chloride and saturated NaCl, dried, and purified to give 14.1 (0.4 g, 59%).
- 10 **Aminoindazole derivative 14.3:** A methylene chloride solution (5 mL) of 14.1 (0.4 g, 0.58 mmol) was treated with TFA (1 mL) at room temperature for 1.5 h, and then concentrated under reduced pressure to give crude 14.2. The crude 14.2 was dissolved in n-BuOH (5 mL) and reacted with hydrazine hydrate (0.58 g, 11.6 mmol) at reflux for 5 h. The reaction

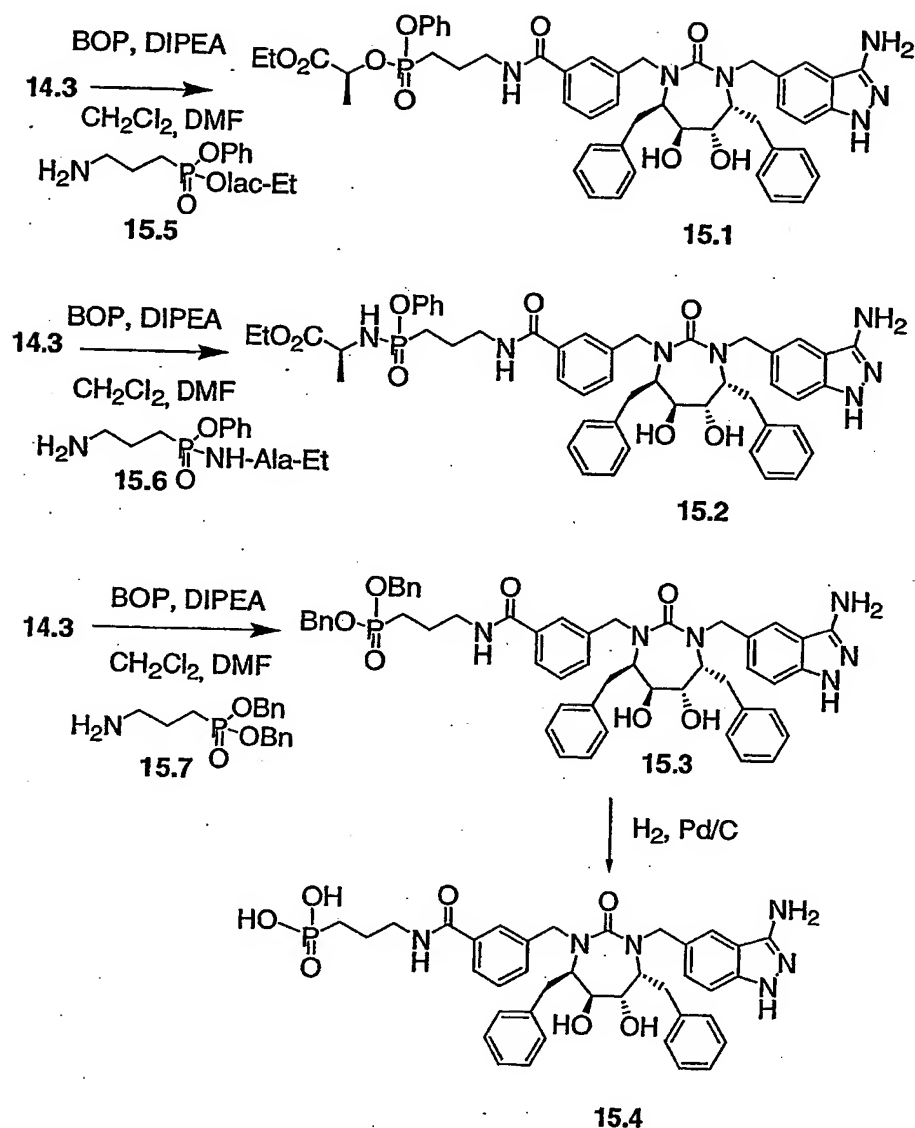
mixture was concentrated under reduced pressure and purified by silica gel chromatography to give the desired product **14.3** (0.37 g, quantitative yield).

**Diethylphosphonate ester 14.4:** A methylene chloride solution (3 mL) of **14.3** (23 mg, 38  $\mu\text{mol}$ ) was reacted with aminopropyl-diethylphosphonate **14.6** (58 mg, 190  $\mu\text{mol}$ ), DIPEA (50 mg, 380  $\mu\text{mol}$ ), and ByBOP (21 mg, 48  $\mu\text{mol}$ ) at room temperature for 2 h, and then concentrated under reduced pressure. The residue was triturated with methylene chloride/hexane. The solid was purified by preparative TLC to give **14.4** (9 mg, 34 %). NMR ( $\text{CDCl}_3 + \sim 10\% \text{CD}_3\text{O}$ ):  $\delta$  7.87 (t, 1H), 7.61 (b, 1H), 7.51 (s, 1H), 7.14-7.2 (m, 10 H), 6.93-7.0 (m, 4H), 4.79 (d, 2H), 3.99-4.04 (m, 4H), 3.38-3.65 (m, 6H), 2.60-3.2 (m, 6 H), 1.70-1.87 (m, 4H), 1.25 (t, 6H). P NMR ( $\text{CDCl}_3 + \sim 10\% \text{CD}_3\text{OD}$ ): 32.7 ppm.

**Diethylphosphonate ester 14.5:** A methylene chloride solution (2 mL) of **14.3** (13 mg, 21  $\mu\text{mol}$ ) was reacted with aminoethyl-diethylphosphonate oxalate **14.7** (23mg, 85  $\mu\text{mol}$ ), DIPEA (22 mg, 170  $\mu\text{mol}$ ), and ByBOP (12 mg, 25  $\mu\text{mol}$ ) at room temperature for 2 h, and then concentrated under reduced pressure. The residue was triturated with methylene chloride/hexane. The solid was purified by preparative TLC to give **14.5** (5mg, 30%). Ms: 783 (M + 1). NMR ( $\text{CDCl}_3 + \sim 10\% \text{CD}_3\text{O}$ ):  $\delta$  7.88 (b, 1H), 7.58 (b, 1H), 7.49 (s, 1H), 7.14-7.2 (m, 10 H), 6.90-7.0 (m, 4H), 4.75 (d, 2H), 3.90-4.04 (m, 4H), 2.50-3.3 (m, 6 H), 1.97-2.08 (m, 2H). P NMR ( $\text{CDCl}_3 + \sim 10\% \text{CD}_3\text{OD}$ ): 30.12 ppm.



## Scheme 15



Monophenol-ethyl lactate phosphonate prodrug 15.1: A methylene chloride/DMF solution (2 mL/0.5 mL) of 14.3 (30 mg, 49  $\mu$ mol) was reacted with aminopropyl-phenol-ethyl lactate phosphonate 15.5 (100 mg, 233  $\mu$ mol), DIPEA (64 mg, 495  $\mu$ mol), and BOP reagent (45 mg, 100  $\mu$ mol) at room temperature for 2 h, and then concentrated under reduced pressure. The residue was triturated with methylene chloride/hexane. The solid was purified by silica gel chromatography to give 15.1 (28 mg, 64 %). NMR (CDCl<sub>3</sub> + ~10 %CD<sub>3</sub>O):  $\delta$  7.83 (b, 1H), 7.59 (b, 1H), 7.51 (s, 1H), 7.14-7.2 (m, 11 H), 6.90-7.0 (m, 4H), 4.75-4.87 (d +

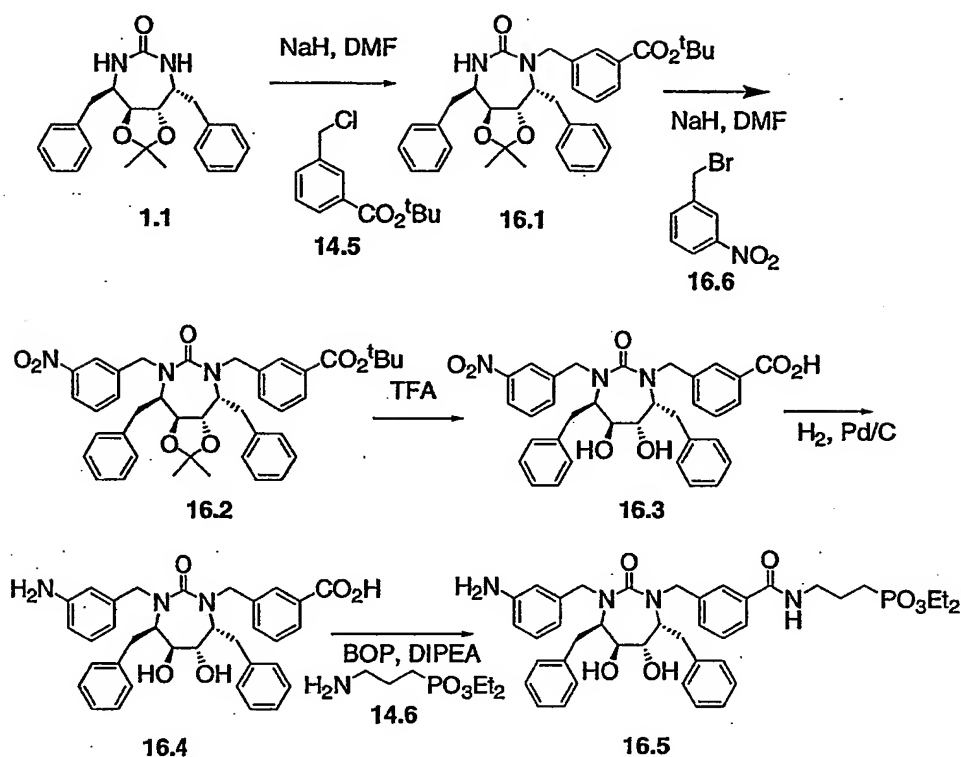
q, 3H), 4.10 (q, 2H), 3.3-3.61 (m, 6H), 2.60-3.2 (m, 6H), 1.92-2.12 (m, 4H), 1.30 (d, 3H), 1.18 (t, 3H). P NMR ( $\text{CDCl}_3$  + ~10 %  $\text{CD}_3\text{OD}$ ): 30.71 ppm. MS: 903 ( $M + 1$ ).

**Phenol-ethyl alanine phosphonate prodrug 15.2:** A methylene chloride/DMF solution (2 mL/0.5 mL) of **14.3** (30 mg, 49  $\mu\text{mol}$ ) was reacted with aminopropyl-phenol-ethyl alanine phosphonate **15.6** (80 mg TFA salt, 186  $\mu\text{mol}$ ), DIPEA (64 mg, 500  $\mu\text{mol}$ ), and BOP reagent (45 mg, 100  $\mu\text{mol}$ ) at room temperature for 2 h, and then concentrated under reduced pressure. The residue was triturated with methylene chloride/hexane. The solid was purified by preparative TLC to give **15.2** (12 mg, 27 %). NMR ( $\text{CDCl}_3$  + ~10 %  $\text{CD}_3\text{O}$ ):  $\delta$  7.91 (b, 1H), 7.61 (b, 1H), 7.52 (s, 1H), 7.14-7.2 (m, 11 H), 6.90-7.0 (m, 4H), 4.75 (d, 2H), 3.82-4.1 (2q, 3H), 3.4-3.65 (m, 6H), 2.60-3.15 (m, 6H), 1.8-2.0 (m, 4H), 1.3 (d, 3H). P NMR ( $\text{CDCl}_3$  + ~10 %  $\text{CD}_3\text{OD}$ ): 32.98 & 33.38 ppm. MS: 902 ( $M + 1$ ).

**Dibenzyl phosphonate 15.3:** A methylene chloride/DMF solution (2 mL/0.5 mL) of **14.3** (30 mg, 49  $\mu\text{mol}$ ) was reacted with aminopropyl dibenzyl phosphonate **15.7** (86 mg TFA salt, 200  $\mu\text{mol}$ ), DIPEA (64 mg, 500  $\mu\text{mol}$ ), and BOP reagent (45 mg, 100  $\mu\text{mol}$ ) at room temperature for 2 h, and then concentrated under reduced pressure. The residue was triturated with methylene chloride/hexane. The solid was purified by preparative TLC to give **15.3** (20 mg, 44%). NMR ( $\text{CDCl}_3$  + ~5%  $\text{CD}_3\text{O}$ ):  $\delta$  7.50-7.58 (m, 2H), 7.14-7.3 (m, 21 H), 6.90-7.0 (m, 4H), 4.7-5.1 (m, 6H), 3.6-3.8 (m, 4H), 3.3-3.55 (m, 2H), 2.60-3.15 (m, 6H), 1.8-2.0 (m, 4H). P NMR ( $\text{CDCl}_3$  + ~5 %  $\text{CD}_3\text{OD}$ ): 33.7 ppm. MS: 907 ( $M + 1$ ).

**Phosphonic diacid 15.4:** An ethanol solution (5 mL) of **15.3** (17 mg, 18.7  $\mu\text{mol}$ ) was hydrogenated at 1 atm in the presence of 10 % Pd/C for 4 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to give the desired product **15.4** (12 mg, 85%). NMR ( $\text{CD}_3\text{O} + 20\% \text{CDCl}_3$ ):  $\delta$  7.88 (b, 1H), 7.59 (b, 1H), 7.6 (s, 1H), 7.1-7.25 (m, 10 H), 6.90-7.1 (m, 4H), 4.8 (d, 2H + water peak), 3.6-3.8 (m, 4H), 3.4-3.5 (m, 2H), 1.85-2.0 (m, 4H).

Scheme 16



**Monobenzyl derivative 16.1:** A DMF solution (4 mL) of 1.1 (0.8 g, 2.2 mmol) was treated with NaH (0.18 g of 60% oil dispersion, 4.4 mmol) for 10 min at room temperature followed by the addition of 14.5 (0.5 g, 2.2 mmol). The resulting solution was reacted at room temperature for 2 h, worked up, and then purified to afford 16.1 (0.48 g, 40%).

**3-Nitrobenzyl cyclic urea derivative 16.2:** A DMF solution (0.5 mL) of 16.1 (65 mg, 117  $\mu$ mol) was treated with NaH (15 mg of 60% oil dispersion, 375  $\mu$ mol) for 10 min at room temperature, followed by the addition of 3-nitrobenzyl bromide (33 mg, 152  $\mu$ mol). The resulting solution was reacted at room temperature for 1 h, worked up, and purified by preparative TLC to afford 16.2 (66 mg, 82%).

**Diol 16.3:** A methylene chloride solution (2 mL) of 16.2 (46 mg, 61  $\mu$ mol) was treated with TFA (0.4 mL) for 2 h at room temperature, and then concentrated under reduced pressure to afford 16.3. This material was used without further purification.

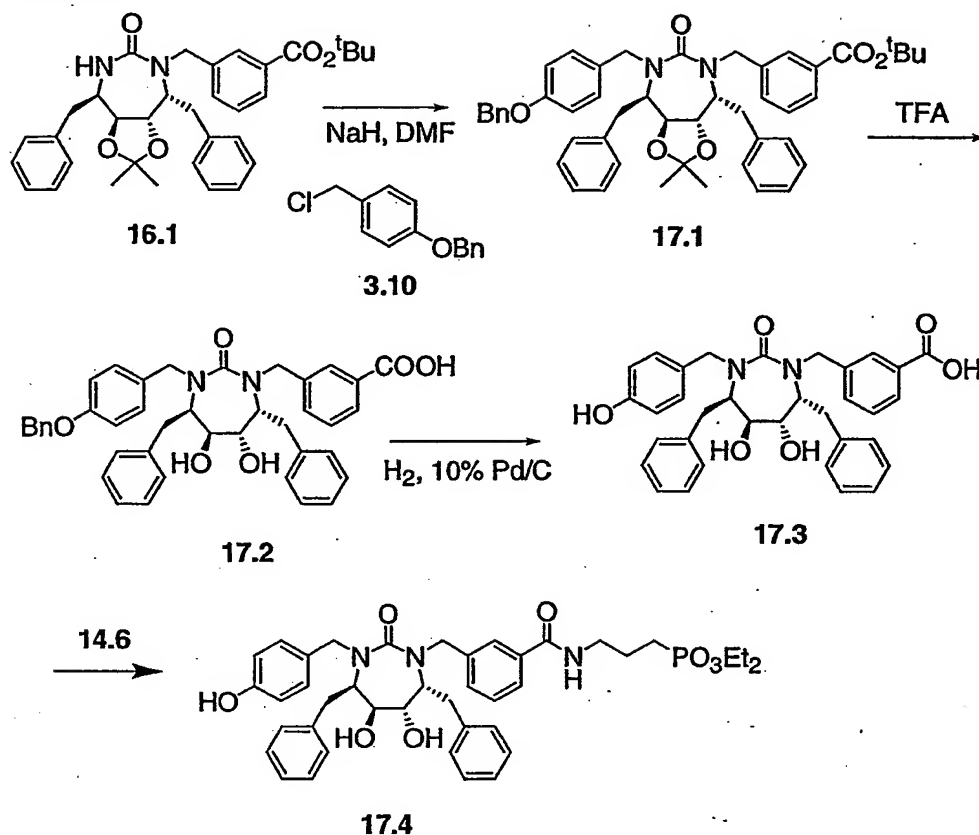
**3-Aminobenzyl cyclic urea 16.4:** An ethyl acetate/ethanol (5 mL/1 mL) solution of **16.3** (crude) was hydrogenated at 1 atm in the presence of 10% Pd/C for 2 h. The catalyst was removed by filtration. The filtrate was concentrated under reduced pressure, and purified by preparative TLC to afford **16.4** (26 mg, 70%, 2 steps).

5

**Diethyl phosphonate 16.5:** A methylene chloride/DMF solution (2 mL/0.5 mL) of **16.4** (24 mg, 42  $\mu$ mol) was reacted with aminopropyl-diethylphosphonate ester TFA salt **14.6** (39 mg, 127  $\mu$ mol), DIPEA (27 mg, 210  $\mu$ mol), and BOP reagent (28 mg, 63  $\mu$ mol) at room temperature for 2 h, and then concentrated under reduced pressure. The residue was purified by preparative TLC to give **16.5** (20.7 mg, 63 %). NMR ( $\text{CDCl}_3$  + ~10 %  $\text{CD}_3\text{O}$ ):  $\delta$  7.62 (b, 1H), 7.51 (s, 1H), 7.0-7.35 (m, 12 H), 6.95 (d, 2H), 6.85 (d, 2H), 4.6-4.71 (2d, 2H), 3.95-4.1 (m, 4H), 3.3-3.55 (m, 3H), 2.60-2.8 (m, 2H), 2.95-3.15 (m, 4 H), 1.85-2.0 (m, 4H), 1.25 (t, 6H). P NMR ( $\text{CDCl}_3$  + ~10 %  $\text{CD}_3\text{OD}$ ): 32.65 ppm.

10

Scheme 17



**p-Benzyloxybenzyl cyclic urea derivative 17.1:** A DMF solution (0.5 mL) of 16.1 (65 mg, 117  $\mu$ mol) was treated with NaH (15 mg of 60% oil dispersion, 375  $\mu$ mol) for 10 min at room temperature, followed by the addition of 4-benzyloxy benzyl chloride 3.10 (35 mg,  $\mu$ mol). The resulting solution was stirred for 2 h at room temperature. The reaction mixture was concentrated under reduced pressure, purified by preparative TLC to generate 17.1 (62 mg, 70%).

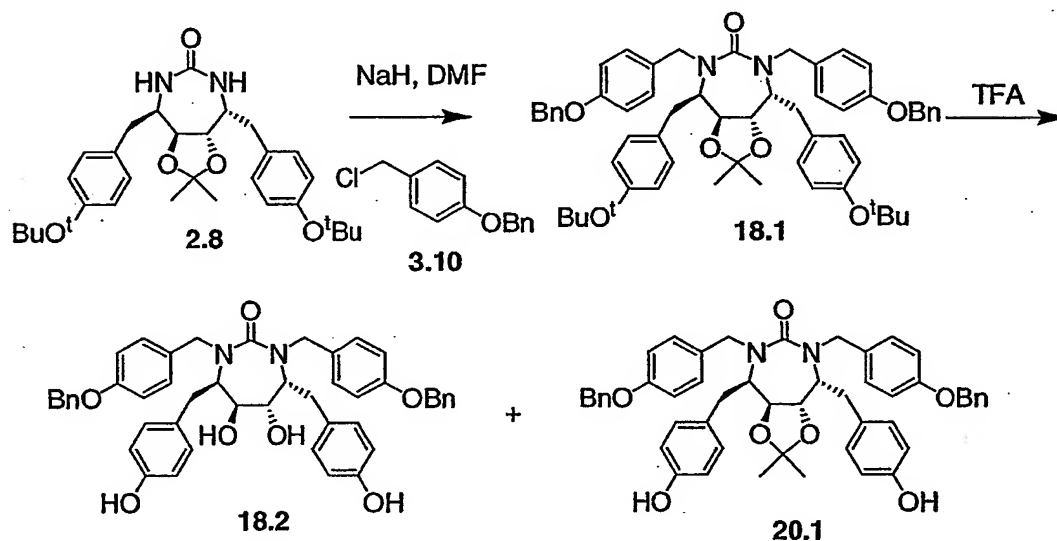
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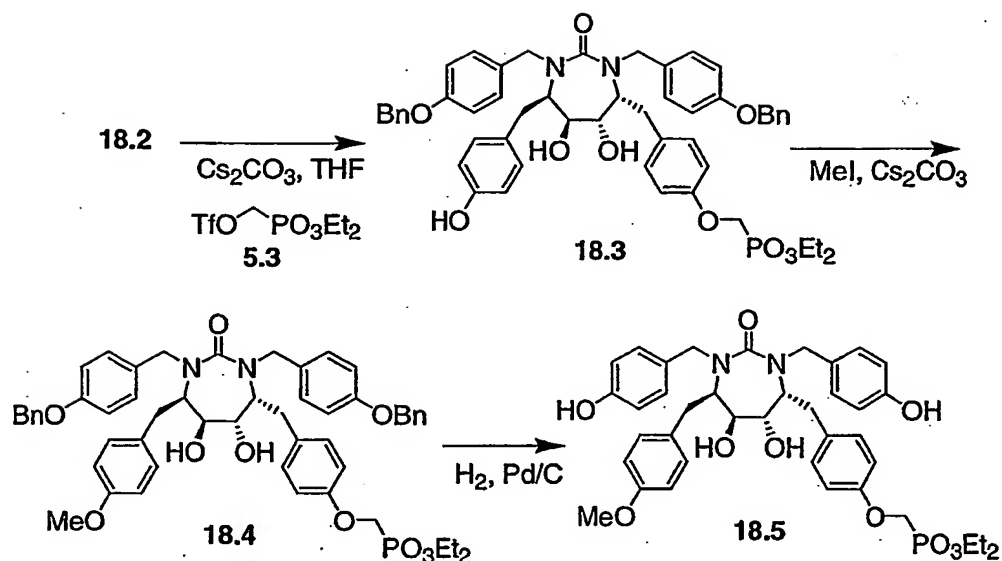
**Diethyl phosphonate 17.3:** A methylene chloride solution (2 mL) of 17.1 (46 mg, 61  $\mu$ mol) was treated with TFA (0.4 mL) for 2 h at room temperature, and then concentrated under reduced pressure to give crude 17.2. An ethyl acetate/ethanol solution (3 mL/2 mL) of the crude 17.2 was then hydrogenated at 1 atm in the presence of 10% Pd/C (10 mg) for 5 h at room temperature. The catalyst was removed by filtration. The filtrate was concentrated under reduced pressure to afford 17.3 (crude).

15

**Diethyl phosphonate cyclic urea 17.4:** A methylene chloride/DMF solution (2 mL/0.5 mL) of 17.3 (25 mg, 42  $\mu$ mol) was reacted with aminopropyl-diethylphosphonate ester TFA salt 14.6 (40 mg, 127  $\mu$ mol), DIPEA (27 mg, 210  $\mu$ mol), and BOP reagent (28 mg, 63  $\mu$ mol) at room temperature for 2 h, and then concentrated under reduced pressure. The residue was  
5 purified by preparative TLC to give 17.4 (14.6 mg, 44 %). NMR ( $\text{CDCl}_3$  + ~10 %  $\text{CD}_3\text{O}$ ):  $\delta$  7.82 (t), 7.62 (d, 1H), 7.51 (s, 1H), 7.05-7.35 (m, 10 H), 6.8-6.95 (2d, 4H), 6.85 (d, 2H), 4.8 (d, 1H), 4.65 (d, 1H), 3.95-4.1 (m, 4H), 3.4-3.75 (m, 6H), 2.60-3.2 (m), 1.85-2.0 (m, 4H), 1.25 (t, 6H). P NMR ( $\text{CDCl}_3$  + ~10 %  $\text{CD}_3\text{OD}$ ): 32.72 ppm.

## 10 Scheme 18





**Dibenzyl derivative 18.1:** A DMF solution (3 mL) of compound 2.8 (0.4 g, 0.78 mmol) was reacted with 60%NaH (0.13 g, 1.96 mmol), 4-benzyloxy benzylchloride 3.10 (0.46 g, 1.96 mmol) and sodium iodide (60 mg, 0.39 mmol) at room temperature for 4 h. The reaction mixture was partitioned between methylene chloride and saturated  $\text{NaHCO}_3$  solution. The organic phase was isolated, dried over  $\text{Na}_2\text{SO}_4$ , concentrated under reduced pressure, and purified by silica gel chromatography to give the desired product 18.1 (0.57 g, 81%).

**Diol derivative 18.2 and diphenol derivative 20.1:** A methylene chloride solution (4 mL) of 18.1 (0.57 g, 0.63 mmol) was treated with TFA (1 mL) at room temperature for 20 min, concentrated under reduced pressure, and purified by silica gel chromatography to give diol derivative 18.2 (133 mg, 28 %) and diphenol derivative 20.1 (288 mg, 57.6%).

**Monophosphonate derivative 18.3:** A THF solution (10 mL) of 18.2 (130 mg, 0.17 mmol) was stirred with cesium carbonate (70 mg, 0.21 mmol) and diethylphosphonate triflate 5.3 (52 mg, 0.17 mmol) at room temperature for 4 h.. The reaction mixture was concentrated under reduced pressure and purified to give 18.3 (64 mg, 41 %), and recovered 18.2 (25 mg, 19%).

20

**Methoxy derivative 18.4:** A THF solution (2 mL) of 18.3 (28 mg, 25  $\mu\text{mol}$ ) was treated with cesium carbonate (25 mg, 76  $\mu\text{mol}$ ) and iodomethane (10 eq. Excess) at room

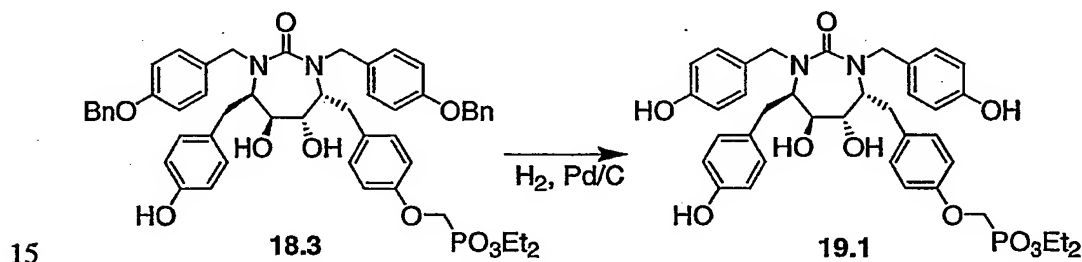
temperature for 5 h. The reaction mixture was concentrated under reduced pressure and partitioned between methylene chloride and saturated  $\text{NaHCO}_3$ . The organic phase was separated, concentrated under reduced pressure and the residue purified by preparative TLC to afford **18.4** (22 mg, 78%).

5

**Diethylphosphonate 18.5**: An ethyl acetate/ethanol (2 mL/2 mL) solution of **18.4** (22 mg, 24  $\mu\text{mol}$ ) was hydrogenated at 1 atm in the presence of 10% Pd/C for 3 h. The catalyst was removed by filtration, the filtrate was concentrated under reduced pressure to give the desired product **18.5** (18 mg, quantitative). NMR ( $\text{CDCl}_3$  + ~10 % $\text{CD}_3\text{O}$ ):  $\delta$  6.7-7.0 (m, 12 H), 6.62-6.69 (m, 4H), 4.65 (d, 1H), 4.50 (d, 1H), 4.18-4.3 (m, 6H), 3.75 (s, 3H), 3.3-3.4 (m, 4H), 2.8-3.0 (m, 6H), 1.30 (t, 6H). P NMR ( $\text{CDCl}_3$  + ~10 % $\text{CD}_3\text{OD}$ ): 20.16 ppm.

10

#### Scheme 19

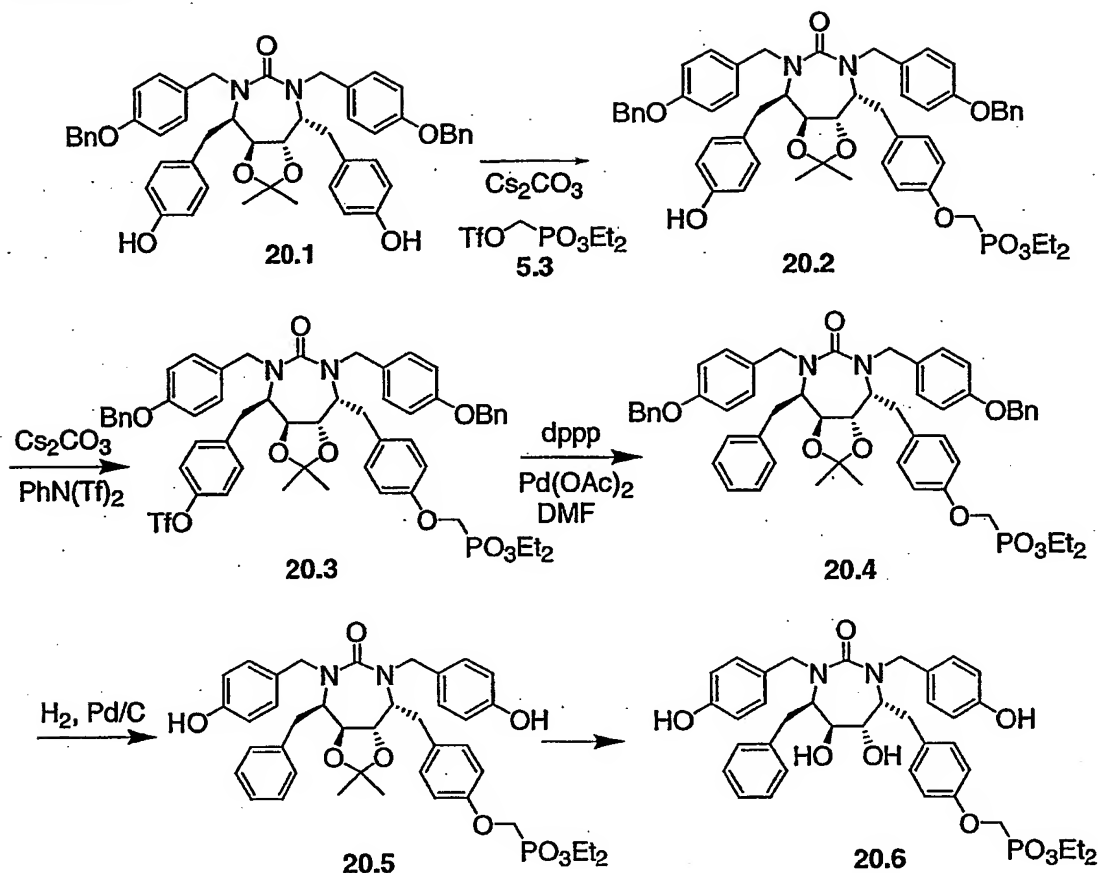


**Diethyl phosphonate 19.1**: An ethyl acetate/ethanol (2 mL/1 mL) solution of **18.3** (14 mg, 15.5  $\mu\text{mol}$ ) was hydrogenated at 1 atm in the presence of 10% Pd/C (5 mg) for 3 h. The catalyst was then removed by filtration, and the filtrate was concentrated under reduced pressure to give the desired product **19.1** (10 mg, 90%). NMR ( $\text{CDCl}_3$  + ~15 % $\text{CD}_3\text{O}$ ):  $\delta$  6.6-7.0 (m, 16 H), 4.5-4.65 (2d, 2H), 4.1-4.3 (m, 6H), 2.7-3.0 (m, 6H), 1.29 (t, 6H). P NMR ( $\text{CDCl}_3$  + ~15 % $\text{CD}_3\text{OD}$ ): 20.12 ppm.

20



Scheme 20

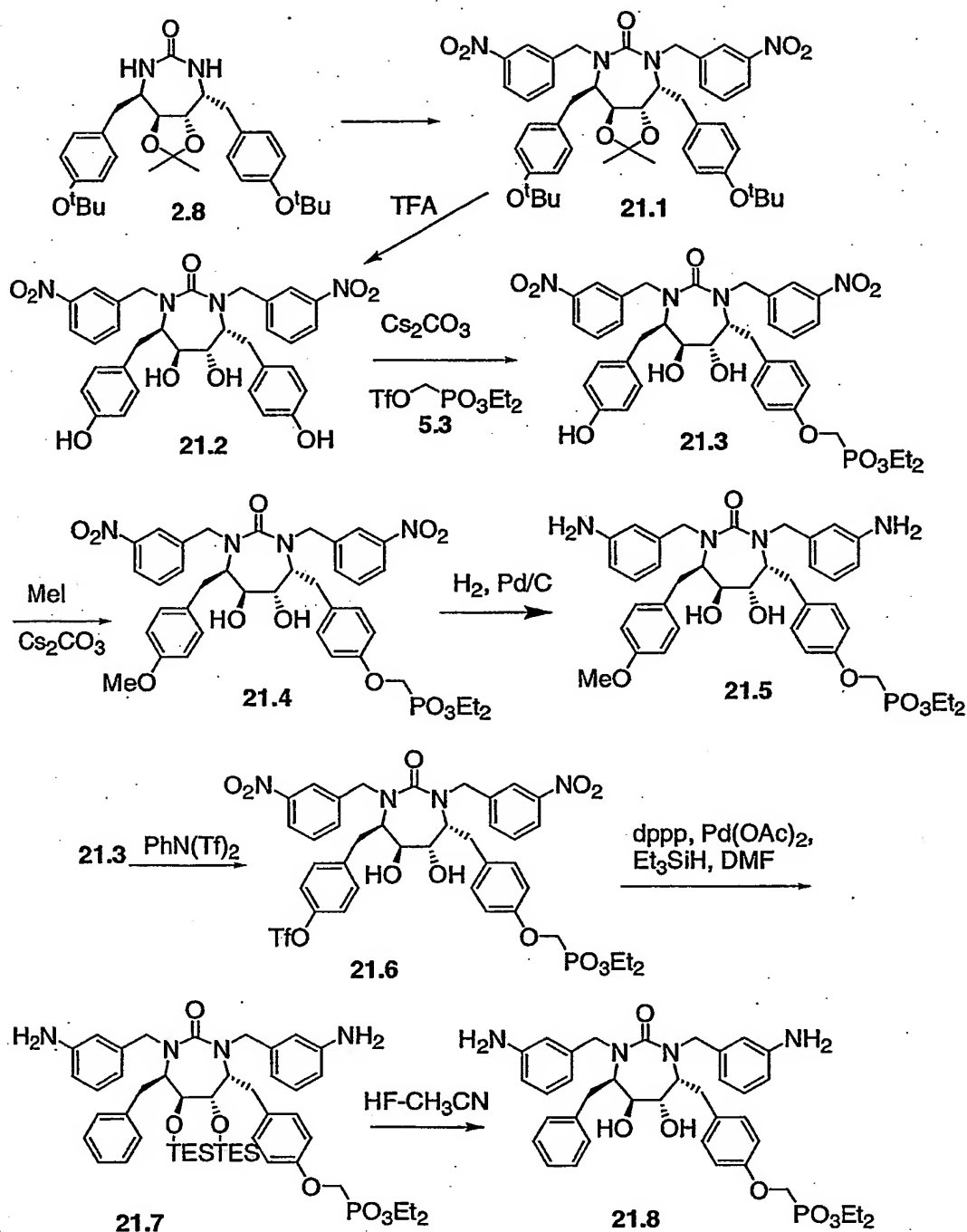


- 5 **Monophosphonate 20.2:** A THF solution (8 mL) of **20.1** (280 mg, 0.36 mmol) was stirred with cesium carbonate (140 mg, 0.43 mmol) and diethylphosphonate triflate **5.3** (110 mg, 0.36 mmol) at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure and purified to give **20.2** (130mg, 39%), and recovered **20.1** (76 mg, 27%).
- 10 **Triflate derivative 20.3:** A THF solution (6 mL) of **20.2** (130 mg, 0.13 mmol) was stirred with cesium carbonate (67 mg, 0.21 mmol) and N-phenyltrifluoromethane-sulfonimide (60mg, 0.17 mmol) at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure and purified to give **20.3** (125 mg, 84%).
- 15 **Benzyl ether 20.4:** To a DMF solution (2 mL) of  $\text{Pd}(\text{OAc})_2$  (60 mg, 267  $\mu\text{mol}$ ), and dppp (105 mg, 254  $\mu\text{mol}$ ) was added **20.3** (120 mg, 111  $\mu\text{mol}$ ) under nitrogen, followed by the addition of triethylsilane (0.3 mL). The resulting solution was stirred at room temperature for

4 h, then concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford **20.4** (94 mg, 92%).

**Diethyl phosphonate 20.6:** An ethyl acetate/ethanol (2 mL/2 mL) solution of **20.4** (28 mg, 30  $\mu$ mol) was hydrogenated at 1 atm in the presence of 10% Pd/C (5 mg) for 3 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to give the desired product **20.5**. The crude product **20.5** was redissolved in methylene chloride (2 mL) and treated with TFA (0.4 mL) and a drop of water. After 1 h stirring at room temperature, the reaction mixture was concentrated under reduced pressure, and  
5  
10 purified by preparative TLC plate to give **20.6** (18 mg, 85 %, 2 steps).  $\delta$  6.6-7.3 (m, 17 H), 4.65 (d, 1H), 4.58 (d, 1H), 4.18-4.3 (m, 6H), 3.3-3.5 (m, 4H), 2.8-3.1 (m), 1.34 (t, 6H). P NMR ( $\text{CDCl}_3$  + ~10 %  $\text{CD}_3\text{OD}$ ): 20.16 ppm. MS: 705 (M + 1).

Scheme 21



**Bis-(3-nitrobenzyl) derivative 21.1:** A DMF solution (2 mL) of compound 2.8 (0.3 g, 0.59 mmol) was reacted with 60%NaH (0.07 g, 1.76 mmol), 3-nitrobenzyl bromide (0.38 g, 1.76 mmol) and sodium iodide (60 mg, 0.39 mmol) at room temperature for 3 h. The reaction

mixture was partitioned between methylene chloride and saturated  $\text{NaHCO}_3$  solution. The organic phase was isolated, dried over  $\text{Na}_2\text{SO}_4$ , concentrated under reduced pressure, and purified by silica gel chromatography to give the desired product **21.1** (0.37 g, 82%).

5 **Diphenol derivative 21.2:** A methylene chloride solution (4 mL) of **21.1** (0.37 g, 0.47 mmol) was treated with TFA (1 mL) at room temperature for 3 h, and then concentrated under reduced pressure, and azeotroped with  $\text{CH}_3\text{CN}$  twice to give diphenol derivative **21.2** (0.3 g, quantitative).

10 **Monophosphonate derivative 21.3:** A THF solution (8 mL) of **18.2** (0.28g, 0.44 mmol) was stirred with cesium carbonate (0.17 g, 0.53 mmol) and diethylphosphonate triflate **5.3** (0.14 g, 0.44 mmol) at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure and purified to give **21.3** (120 mg, 35%), and recovered **21.2** (150 mg, 53%).

15

**Methoxy derivative 21.4:** A THF solution (2 mL) of **21.3** (9 mg, 11  $\mu\text{mol}$ ) was treated with cesium carbonate (15 mg, 46  $\mu\text{mol}$ ) and iodomethane (10 eq. Excess) at room temperature for 6 h. The reaction mixture was concentrated under reduced pressure and partitioned between methylene chloride and saturated  $\text{NaHCO}_3$ . The organic phase was separated, dried over  
20 sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC to afford **21.4** (9 mg)

**Diethylphosphonate 21.5:** A ethyl acetate/ethanol (2 mL/0.5 mL) solution of **21.4** (9 mg, 11  $\mu\text{mol}$ ) was hydrogenated at 1 atm in the presence of 10% Pd/C for 4 h. The catalyst was  
25 removed by filtration, and the filtrate was concentrated under reduced pressure to give the desired product **21.5** (4.3 mg, 49%, 2 steps). NMR ( $\text{CDCl}_3$  + ~10 %  $\text{CD}_3\text{O}$ ):  $\delta$  7.0-7.10 (m, 6 H), 6.8-6.95 (m, 4H), 6.5-6.6 (m, 4H), 6.4-6.45 (m, 2H), 4.72 (d, 2H), 4.18-4.3 (m, 6H). 3.72 (s, 3H), 3.4-3.5 (m, 4H), 2.8-3.0 (m, 6H), 1.34 (t, 6H). P NMR ( $\text{CDCl}_3$  + ~10 %  $\text{CD}_3\text{OD}$ ): 19.93 ppm.

30

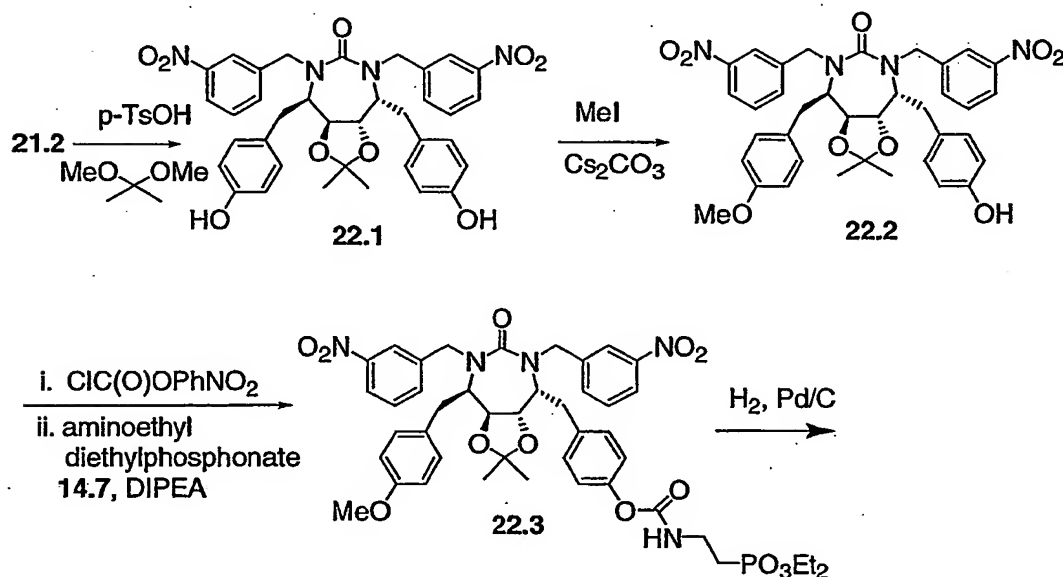
**Triflate 21.6:** A THF solution (6 mL) of **21.3** (0.1g, 0.14 mmol), cesium carbonate (0.07 g, 0.21 mmol), and N-phenyltrifluoromethane-sulfonimide (60mg, 0.17 mmol) was stirred at

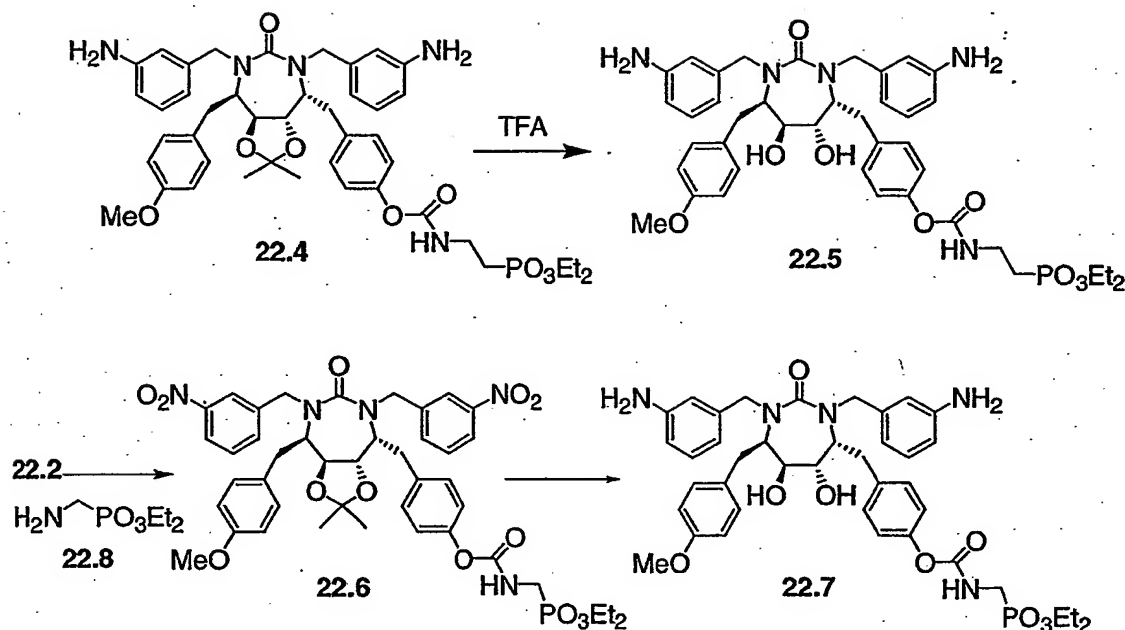
room temperature for 4 h, and then concentrated under reduced pressure, and worked up. The residue was purified by silica gel chromatography to give **21.6** (116 mg, 90%).

**Diamine 21.7:** A DMF solution (2 mL) of **21.6** (116 mg, 127  $\mu\text{mol}$ ), dppp (60 mg, 145  $\mu\text{mol}$ ), and  $\text{Pd}(\text{OAc})_2$  (30 mg, 134  $\mu\text{mol}$ ) was stirred under nitrogen, followed by addition of triethylsilane (0.3 mL), and reacted for 4 h at room temperature. The reaction mixture was worked up and purified to give **21.7** (50 mg).

**Diethyl phosphonate 21.8:** An acetonitrile solution (1 mL) of crude **21.7** (50 mg) was treated with 48% HF (0.1 mL) for 4 h. The reaction mixture was concentrated under reduced pressure, and purified to give **21.8** (10 mg, 11% (2 steps)). NMR ( $\text{CDCl}_3$  + ~10%  $\text{CD}_3\text{O}$ ):  $\delta$  7.05-7.30 (m, 9 H), 6.8-6.95 (d, 2H), 6.4-6.6 (m, 6H), 4.72 (d, 2H), 4.18-4.3 (m, 6H), 3.4-3.5 (m, 4H), 2.8-3.0 (m, 6H), 1.34 (t, 6H). P NMR ( $\text{CDCl}_3$  + ~10 %  $\text{CD}_3\text{OD}$ ): 19.83 ppm.

## 15 Scheme 22





**Acetonide 22.1:** An acetone/2,2-dimethoxypropane solution (15 mL/5 mL) of compound 21.2 (240 mg, 0.38 mmol) and pyridinium toluenesulfonate (10 mg) was heated at reflux for 30 min. After cooled to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was partitioned between methylene chloride and saturated NaHCO<sub>3</sub> aqueous solution, dried, concentrated under reduced pressure and purified to afford 22.1 (225 mg, 88%).

**Monomethoxy derivative 22.2:** A THF solution (10 mL) of 22.1 (225 mg, 0.33 mmol) was treated with cesium carbonate (160 mg, 0.5 mmol) and iodomethane (52 mg, 0.37 mmol) at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and purified by preparative silica gel column chromatography to afford 22.2 (66 mg, 29%) and recovered starting material 22.1 (25 mg, 11%).

15

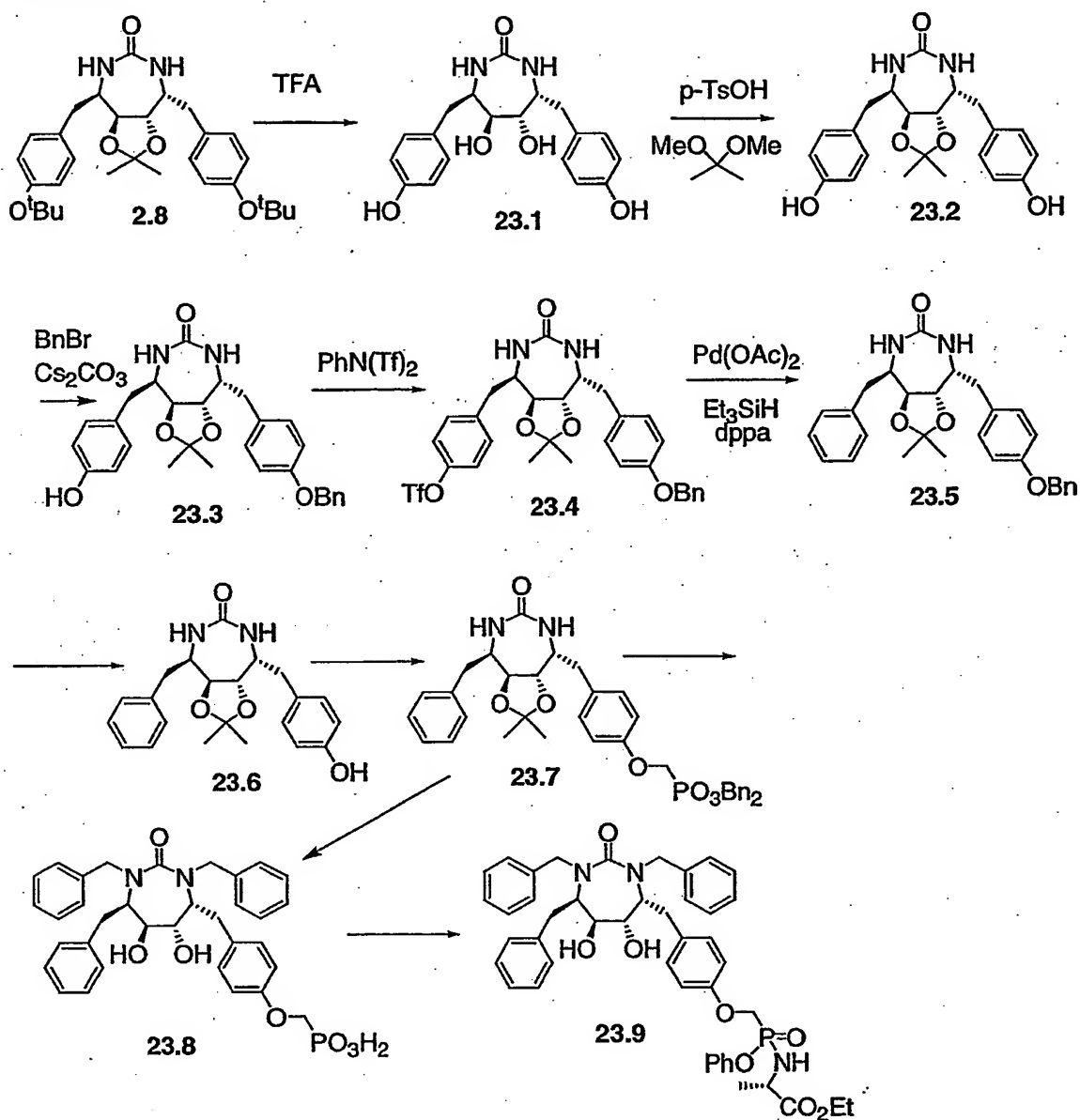
**Diethyl phosphonate 22.3:** A methylene chloride solution (2 mL) of 22.2 (22 mg, 32 μmol), DIPEA (9 mg, 66 μmol), and p-nitrophenyl chloroformate (8 mg, 40 μmol) was stirred at room temperature for 30 min. The resulting reaction mixture was reacted with DIPEA (10 mg, 77 μmol), and aminoethyl diethylphosphonate 14.7 (12 mg, 45 μmol) at room temperature overnight. The reaction mixture was washed with 5% citric acid solution, saturated NaHCO<sub>3</sub>, dried, and purified by preparative TLC to afford 22.3 (12 mg, 43%).

20

**Bis(3-aminobenzyl)-diethylphosphonate ester 22.5:** An ethyl acetate/*t*-BuOH (4 mL/2 mL) solution of 22.3 (12 mg, 13  $\mu$ mol) was hydrogenated at 1 atm in the presence of 10% Pd/C 95 mg) at room temperature for 5 h. The catalyst was removed by filtration. The filtrate was concentrated under reduced pressure, and purified by preparative TLC to give 22.4 (8 mg, 72%). A methylene chloride solution (0.5 mL) of 22.4 (8 mg) was treated with TFA (0.1 mL) at room temperature for 1 h., concentrated under reduced pressure, and then azeotroped with CH<sub>3</sub>CN twice to afford 22.5 (8.1 mg, 81%). NMR (CDCl<sub>3</sub> + ~10 %CD<sub>3</sub>OD):  $\delta$  7.2 (d, 1H), 6.95-7.15 (m, 6H), 6.75-6.9 (m, 5 H), 4.66 (d, 1H), 4.46 (d, 1H), 4.06-4.15 (m, 4H). 3.75 (s, 3H), 3.6-3.7 (m, 4H), 2.6-3.1 (m, 6H), 2.0-2.1 (m, 2H), 1.30 (t, 6H). P NMR (CDCl<sub>3</sub> + ~10 %CD<sub>3</sub>OD): 29.53 ppm. MS: 790 (M + 1).

**Bis(3-aminobenzyl) diethylphosphonate ester 22.7:** Compound 22.7 was prepared from 22.2 (22 mg, 32  $\mu$ mol) and aminomethyl diethylphosphonate 22.8 as shown above for the preparation of 22.5 from 22.2. NMR (CDCl<sub>3</sub> + ~10 %CD<sub>3</sub>OD):  $\delta$  7.24 (d, 1H), 6.8-7.12 (m, 11H), 4.66 (d, 1H), 4.45 (d, 1H), 4.06-4.15 (m, 4H). 3.75 (s, 3H), 2.6-3.1 (m, 6H), 1.30 (t, 6H). P NMR (CDCl<sub>3</sub> + ~10 %CD<sub>3</sub>OD): 22.75 ppm. MS: 776 (M + 1).

Scheme 23



5

**Diol 23.1:** To a solution of compound 2.8 (2.98 g, 5.84 mmol) in methylene chloride (14 mL) was added TFA (6 mL). The resulted mixture was stirred at room temperature for 2 h. Methanol (5 mL) and additional TFA (5 mL) were added. The reaction mixture was stirred for additional 4 h and then concentrated under reduced pressure. The residue was washed with hexane/ethyl acetate (1:1) and dried to afford compound 23.1 (1.8 g, 86%) as an off-white solid.

10



**Benzyl ether 23.3:** To a solution of compound 23.1 (1.8 g, 5.03 mmol) in DMF (6 mL) and 2,2-dimethoxyl propane (12 mL) was added p-toluenesulfonic acid monohydrate (0.095 g, 0.5 mmol). The resultant mixture was stirred at 65°C for 3 h. The excess 2,2-dimethoxyl propane was slowly distilled. The reaction mixture was cooled to room temperature and  
5 charged with THF (50 mL), benzyl bromide (0.8 mL, 6.73 mmol) and cesium carbonate (2.0 g, 6.13 mmol). The resulted mixture was stirred at 65°C for 16 h. The reaction was quenched with acetic acid aqueous solution (4%, 100 mL) at 0°C, and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford desired  
10 mono protected compound 23.3 (1.21 g, 49%).

**Benzyl ether 23.5:** To a solution of compound 23.3 (0.65 g, 1.33 mmol) and N-phenyltrifluoromethanesulfonimide (0.715 g, 2 mmol) in THF (12 mL) was added cesium carbonate (0.65 g, 2 mmol). The mixture was stirred at room temperature for 3 h. The  
15 reaction mixture was filtered through a pad of silica gel and concentrated under reduced pressure. The residue was purified on silica gel chromatography to give triflate 23.4 (0.85 g). To a solution of 1,3-bis(diphenylphosphino)propane (0.275g, 0.66 mmol) in DMF (10 mL) was added palladium(II) acetate (0.15 g, 0.66 mmol) under argon. This mixture was stirred for 2 min. and then added to triflate 23.4. After stirring for 2 min., triethylsilane was added  
20 and the resulted mixture was stirred for 1.5 h. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel to afford compound 23.5 (0.56 g, 89%).

**Phenol 23.6:** A solution of 23.5 (0.28 g, 0.593 mmol) in ethyl acetate (5 mL) and isopropyl alcohol (5 mL) was treated with 10% Pd/C (0.05g) and stirred under a hydrogen atmosphere (balloon) for 16 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to yield 23.6 (0.22 g, 97%) as a white solid.  
25

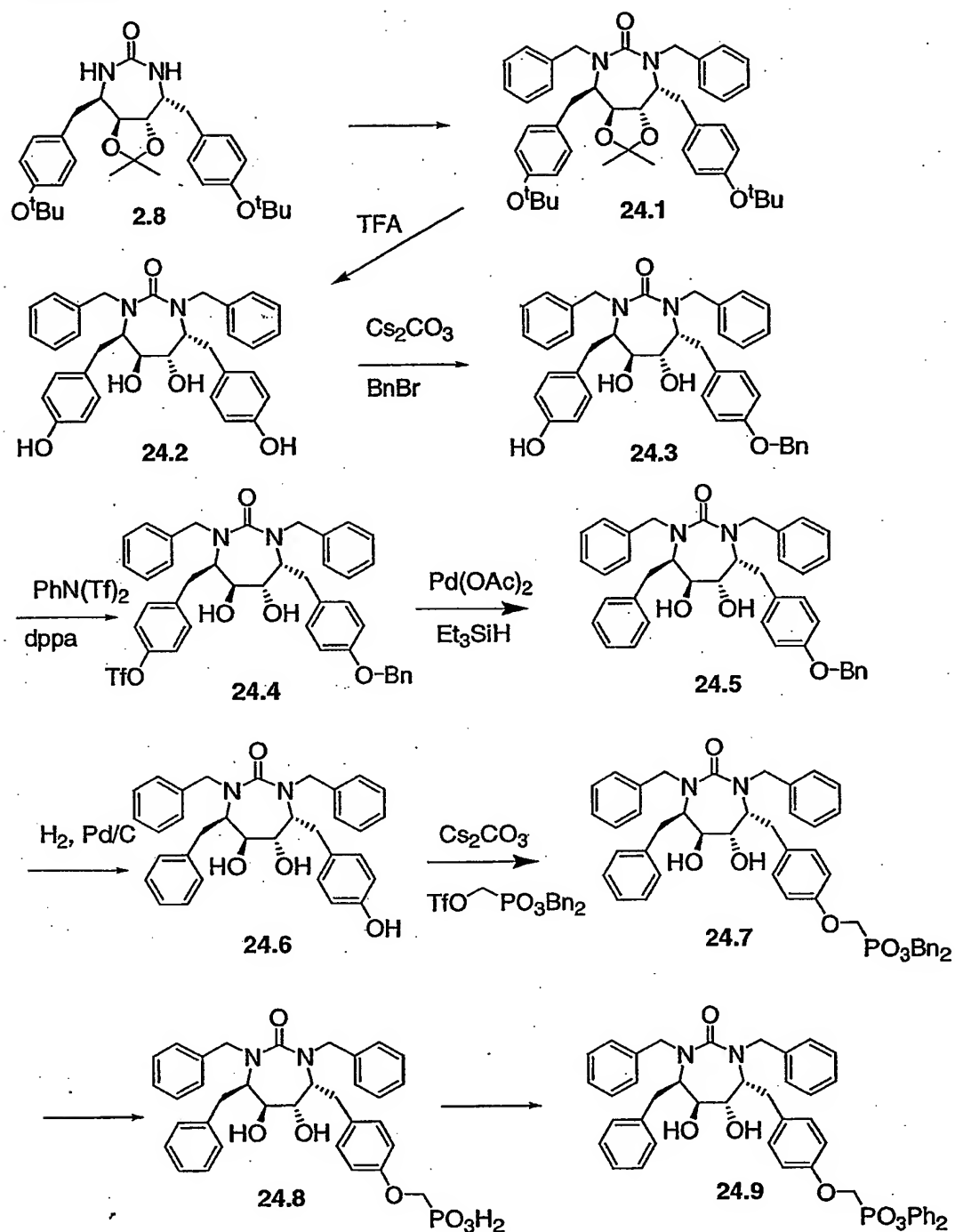
**Dibenzyl phosphonate 23.7:** To a solution of compound 23.6 (0.215 g, 0.563 mmol) in THF (10 mL) was added dibenzyl triflate 3.11 (0.315 g, 0.74 mmol) and cesium carbonate (0.325g, 1 mmol). The mixture was stirred at room temperature for 2 h, then diluted with ethyl acetate and washed with water. The organic phase was dried over magnesium sulfate, filtered and  
30

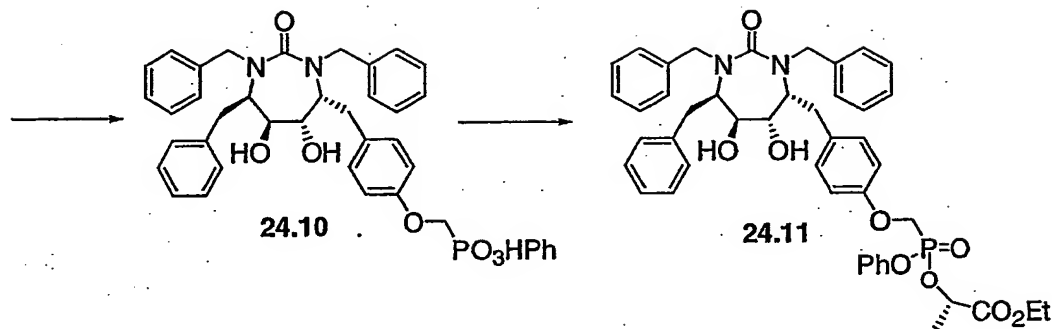
concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford compound 23.7 (0.31 g, 84%).

5 **Diphenyl ester 23.8:** A solution of compound 23.7 (0.3 g, 0.457 mmol) and benzyl bromide (0.165 mL, 1.39 mmol) in THF (10 mL) was treated with potassium *tert*-butoxide (1M/THF, 1.2 mL) for 0.5 h. The mixture was diluted with ethyl acetate and washed with HCl (0.2N). The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and treated with 10% Pd/C (0.05 g) under hydrogen atmosphere (balloon) for 16 h. The catalyst was removed by  
10 filtration and the filtrate was concentrated under reduced pressure. The residue was treated with TFA (1 mL) in methanol (5 mL) for 1 h, and then concentrated under reduced pressure. The residue was dissolved in pyridine (1 mL) and mixed with phenol (0.45 g, 4.8 mmol) and 1,3-dicyclohexylcarbodiimide (0.38 g, 1.85 mmol). The mixture was stirred at 70°C for 2 h, and then concentrated under reduced pressure. The residue was partitioned between ethyl  
15 acetate and HCl (0.2N). The organic phase was dried over magnesium sulfate, filtered and concentrated. The residue was purified by chromatography on silica gel to afford compound 23.8 (0.085 g, 24%).

**Mono amidate 23.9:** To a solution of 23.8 (0.085g, 0.11 mmol) in acetonitrile (1 mL) was  
20 added sodium hydroxide (1N, 0.25 mL) at 0°C. After stirred at 0°C for 1 h, the mixture was acidified with Dowex resin to pH = 3, and filtered. The filtrate was concentrated under reduced pressure. The residue was dissolved in pyridine (0.5 mL) and mixed with L-alanine ethyl ester hydrochloride (0.062 g, 0.4 mmol) and 1,3-dicyclohexyl-carbodiimide (0.125 g, 0.6 mmol). The mixture was stirred at 60°C for 0.5 h, and then concentrated under reduced  
25 pressure. The residue was partitioned between ethyl acetate and HCl (0.2N). The organic phase was dried over magnesium sulfate, filtered and concentrated. The residue was purified by HPLC (C-18, 65% acetonitrile / water) to afford compound 23.9 (0.02 g, 23%). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.2 (m, 3H), 1.4 (m, 3H), 1.8 (brs, 2H), 2.8-3.1 (m, 6H), 3.5-3.7 (m, 4H), 3.78 (m, 1H), 4.0-4.18 (m, 2H), 4.2-4.4 (m, 3H), 4.9 (m, 2H), 6.8-7.4 (m, 24H). <sup>31</sup>P NMR (CDCl<sub>3</sub>): d  
30 20.9, 19.8. MS: 792 (M+1).

Scheme 24





- Di-tert butyl ether 24.1:** To a solution of compound 2.8 (0.51 g, 1 mmol) and benzyl bromide (0.43g, 2.5 mmol) in THF (6 mL) was added potassium *tert*-butoxide (1M/THF, 2.5 mL). The mixture was stirred at room temperature for 0.5 h, then diluted with ethyl acetate and washed with water. The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford compound 24.1 (0.62 g, 90%).
- 10 **Diol 24.2:** To a solution of compound 24.1 (0.62 g, 0.9 mmol) in methylene chloride (4 mL) was added TFA (1 mL) and water (0.1 mL). The mixture was stirred for 2 h, and then concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford compound 24.2 (0.443g, 92%).
- 15 **Benzyl ether 24.3:** Compound 24.3 was prepared in 46% yield according to the procedure described in Scheme 23 for the preparation of 23.3.
- Triflate 24.4:** Compound 24.4 was prepared in 95% yield according to the procedure described in Scheme 23 for the preparation of 23.4.
- 20 **Benzyl ether 24.5:** Compound 24.5 was prepared in 93% yield according to the procedure described in Scheme 23 for the preparation of 23.5.

**Phenol 24.6:** Compound 24.6 was prepared in 96% yield according to the procedure described in Scheme 23 for the preparation of 23.6 from 23.5.

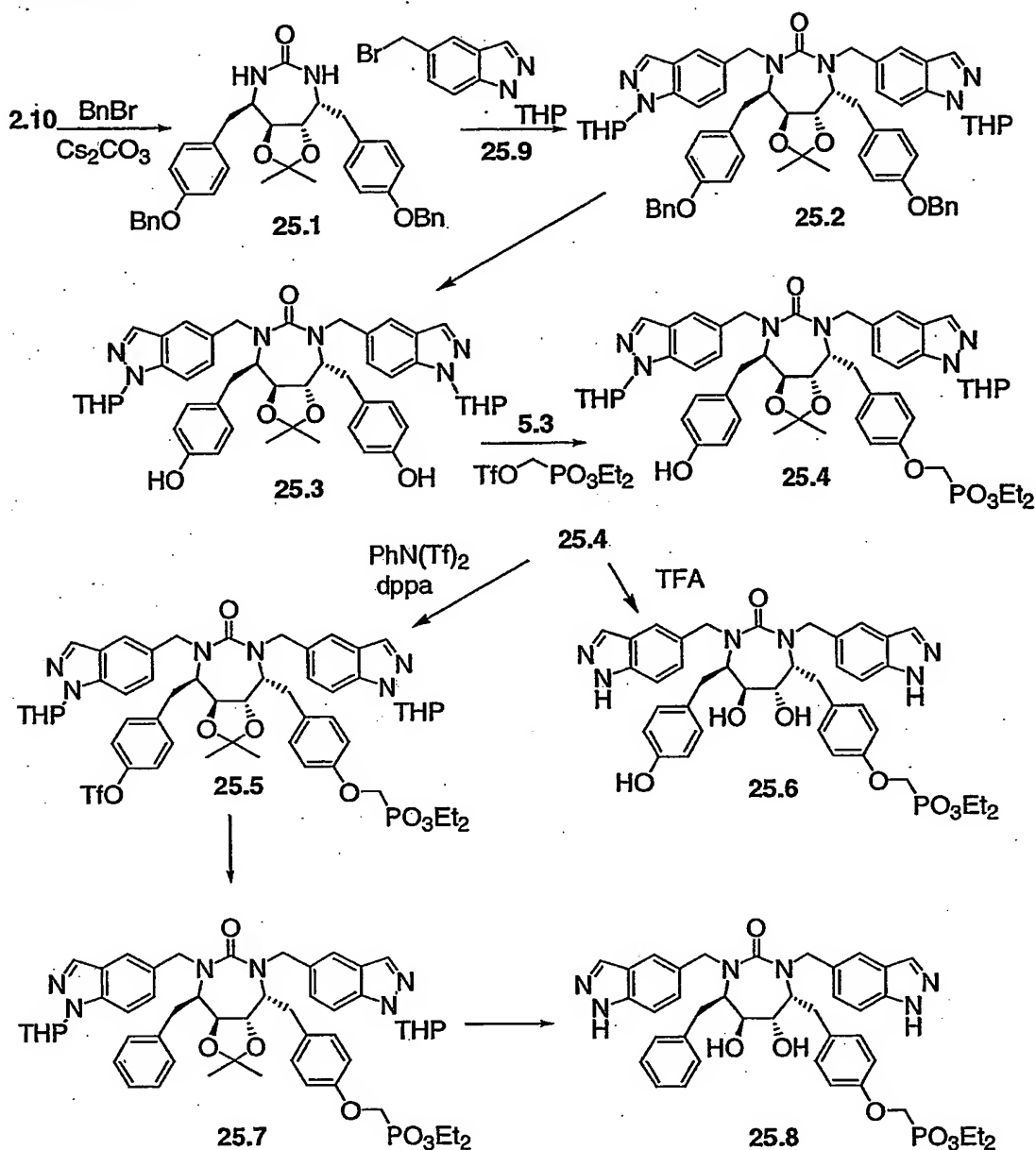
**Dibenzyl phosphonate 24.7:** Compound 24.7 was prepared in 82% yield according to the procedure described in Scheme 23 for the preparation of 23.7.

**Diacid 24.8:** A solution of 24.7 (0.16 g, 0.207 mmol) in ethyl acetate (4 mL) and isopropyl alcohol (4 mL) was treated with 10% Pd/C (0.05g) and stirred under a hydrogen atmosphere (balloon) for 4 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to yield 24.8 (0.125 g, 98%) as a white solid.

**Diphenyl ester 24.9:** To a solution of compound 24.8 (0.12 g, 0.195 mmol) in pyridine (1 mL) was added phenol (0.19 g, 2 mmol) and 1,3-dicyclohexylcarbodiimide (0.206 g, 1 mmol). The mixture was stirred at 70°C for 2 h, and then concentrated under reduced pressure. The residue was partitioned between ethyl acetate and HCl (0.2N). The organic phase was dried over magnesium sulfate, filtered and concentrated. The residue was purified by chromatography on silica gel to afford compound 24.9 (0.038 g, 25%).

**Mono lactate 24.11:** Compound 24.9 was converted, via compound 24.10, into compound 24.11 in 36% yield according to the procedure described in Scheme 23 for the preparation of 23.9 except utilizing the ethyl lactate ester in place of L-alanine ethyl ester. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.05 (t, J = 8 Hz, 1.5H), 1.1 (t, J = 8 Hz, 1.5H), 1.45 (d, J = 8 Hz, 1.5H), 1.55 (d, J = 8 Hz, 1.5H), 2.6 (brs, 2H), 2.9-3.1 (m, 6H), 3.5-3.65 (m, 4H), 4.15-4.25 (m, 2H), 4.4-4.62 (m, 2H), 4.9 (m, 2H), 5.2 (m, 1H), 6.9-7.4 (m, 24H). <sup>31</sup>P NMR (CDCl<sub>3</sub>): δ 17.6, 15.5. MS: 793 (M+1).

Scheme 25



5 **Dibenzyl ether 25.1:** The protection reaction of compound 2.10 with benzyl bromide was carried out in the same manner as described in Scheme 23 to afford compound 25.1.

**Bis indazole 25.2:** The alkylation of compound 25.1 with bromide 25.9 was carried out in the same manner as described in Scheme 23 to afford compound 25.2 in 96% yield.

**Diol 25.3:** A solution of **25.2** (0.18 g, 0.178 mmol) in ethyl acetate (5 mL) and isopropyl alcohol (5 mL) was treated with 20% Pd(OH)<sub>2</sub>/C (0.09g) and stirred under a hydrogen atmosphere (balloon) for 24 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to afford **25.3** in quantitative yield.

5

**Diethyl phosphonate 25.4:** To a solution of compound **25.3** (0.124 g, 0.15 mmol) in acetonitrile (8 mL) and DMF (1 mL) was added potassium tert-butoxide (0.15 mL, 1M/THF). The mixture was stirred for 10 min. to form a clear solution. Diethyl triflate **5.3** (0.045 g, 0.15 mmol) was added to the reaction mixture. After stirred for 0.5 h, the reaction mixture was diluted with ethyl acetate and washed with HCl (0.1N). The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford compound **25.4** (0.039 g, 55% (based on recovered starting material: 0.064 g, 52%).

10

**Bisindazole 25.6:** A mixture of compound **25.4** (0.027 g), ethanol (1.5 mL), TFA (0.6 mL) and water (0.5 mL) was stirred at 60°C for 18 h. The mixture was concentrated under reduced pressure, and the residue was purified by HPLC to afford compound **25.6** as a TFA salt (0.014 g, 51%). <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 1.4 (t, J = 8 Hz, 6H), 2.9 (m, 4H), 3.2 (m, 2H), 3.58 (brs, 2H), 3.65 (m, 2H), 4.25 (m, 4H), 4.42 (d, J = 10 Hz, 2H), 4.85 (m, 2H), 6.75 (d, J = 9 Hz, 2H), 6.9 (m, 4H), 7.0 (d, J = 9 Hz, 2H), 7.4-7.6 (m, 6H), 8.1 (brs, 2H). <sup>31</sup>P NMR (CD<sub>3</sub>OD): δ 20.8. MS: 769 (M+1).

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**Diethyl phosphonate 25.7:** Compound **25.4** was converted into compound **25.7** in 76% yield according to the procedures described in Scheme 23 for the conversion of **23.3** into **23.5**.

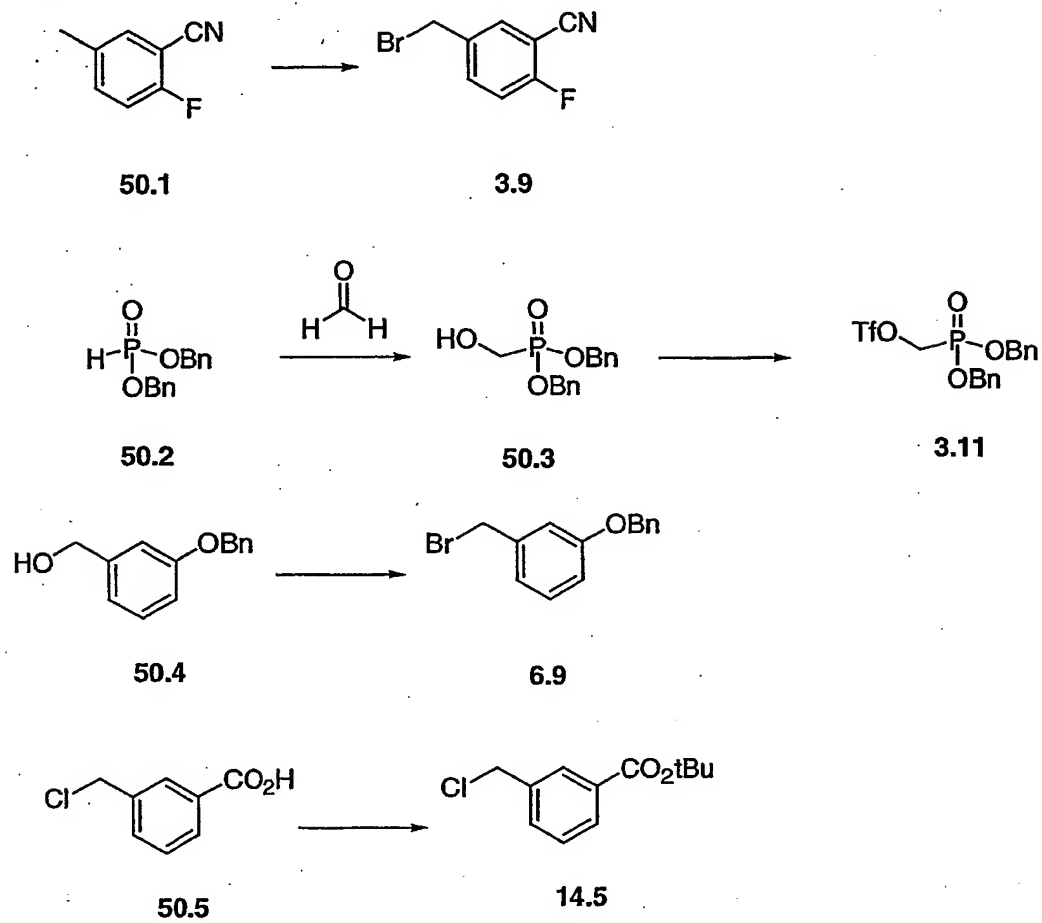
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**Bis indazole 25.8:** Compound **25.7** (0.029 g) was treated in the same manner as compound **25.4** in the preparation of **25.6** to afford compound **25.8** as a TFA salt (0.0175 g, 59%). <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 1.4 (t, J = 8 Hz, 6H), 3.0 (m, 4H), 3.15 (d, J = 14 Hz, 1H), 3.25 (d, J = 14 Hz, 1H), 3.58 (brs, 2H), 3.65 (m, 2H), 4.25 (m, 4H), 4.42 (d, J = 10 Hz, 2H), 4.85 (m, 2H), 6.9 (d, J = 9 Hz, 2H), 7.0 (d, J = 9 Hz, 2H), 7.1 (d, J = 7 Hz, 2H), 7.2-7.6 (m, 9H), 8.1 (brs, 2H). <sup>31</sup>P NMR (CD<sub>3</sub>OD): δ 20.8. MS: 753 (M+1).

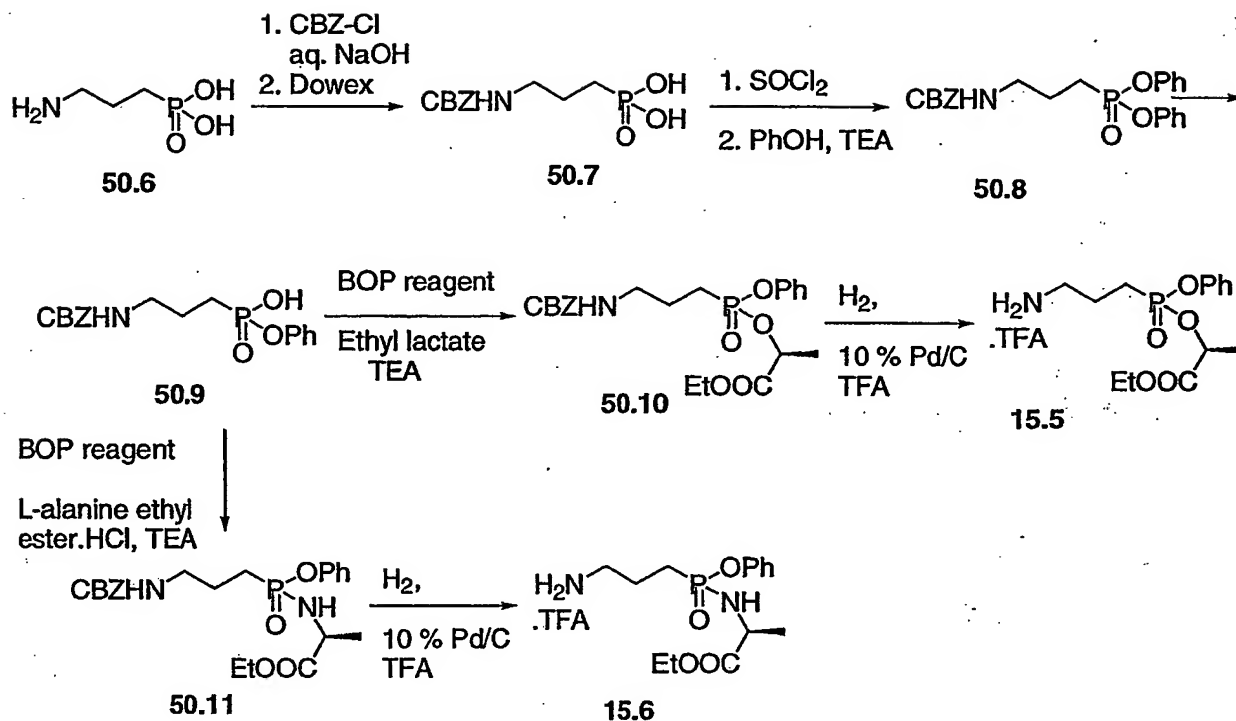
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## Preparation of Alkylating and Phosphonate Reagents

Scheme 50







**3-cyano-4-fluoro-benzylbromide 3.9:** The commercially available 2-fluoro-4-methylbenzonitrile **50.1** (10 g, 74 mmol) was dissolved in carbon tetrachloride (50 mL) and then treated with NBS (16 g, 90 mmol) followed by AIBN (0.6 g, 3.7 mmol). The mixture was stirred at 85°C for 30 min and then allowed to cool to room temperature. The mixture was filtered and the filtrate concentrated under reduced pressure. The residue was purified by silica gel eluting with 5-20% ethyl acetate in hexanes to give **3.9** (8.8 g, 56%).

**4-benzyloxy benzyl chloride 3.10** is purchased from Aldrich

**Dibenzyl triflate 3.11:** To a solution of dibenzyl phosphite **50.2** (100 g, 381 mmol) and formaldehyde (37% in water, 65 mL, 860 mmol) in THF (200 mL) was added TEA (5 mL, 36 mmol). The resulted mixture was stirred for 1 h, and then concentrated under reduced pressure. The residue was dissolved in methylene chloride and hexane (1:1, 300 mL), dried over sodium sulfate, filtered through a pad of silica gel (600 g) and eluted with ethyl acetate and hexane (1:1). The filtrate was concentrated under reduced pressure. The residue **50.3** (95 g) was dissolved in methylene chloride (800 mL), cooled to -78°C and then charged with pyridine (53 mL, 650 mmol). To this cooled solution was slowly added trifluoromethanesulfonic anhydride (120 g, 423 mmol). The resulted reaction mixture was

stirred and gradually warmed up to  $-15^{\circ}\text{C}$  over 1.5 h period of time. The reaction mixture was cooled down to about  $-50^{\circ}\text{C}$ , diluted with hexane-ethyl acetate (2:1, 500 mL) and quenched with aqueous phosphoric acid (1M, 100 mL) at  $-10^{\circ}\text{C}$  to  $0^{\circ}\text{C}$ . The mixture diluted with hexane-ethyl acetate (2:1, 1000 mL). The organic phase was washed with water, dried  
5 over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford dibenzyl triflate 3.11 (66 g, 41%) as a colorless oil.

Diethyl triflate 5.3 is prepared as described in Tet Lett. 1986, 27, p1477-1480

10 **3-Benzyloxybenzylbromide 6.9:** To a solution of triphenyl phosphine (15.7 g, 60 mmol) in THF (150 mL) was added a solution of carbon tetrabromide (20 g, 60 mmol) in THF (50 mL). A precipitation was formed and stirred for 10 min. A solution of 3-benzyloxybenzyl alcohol 50.4 (10 g, 46.7 mmol) was added. After stirred for 1.5 h, the reaction mixture was  
15 filtered and concentrated under reduced pressure. The majority of triphenyl phosphine oxide was removed by precipitation from ethyl acetate-hexane. The crude product was purified by chromatography on silica gel and precipitation from hexane to give the desired product 3-Benzyloxybenzylbromide 6.9 (10 g, 77%) as a white solid.

20 **t-Butyl-3-chloromethyl benzoate 14.5:** A benzene solution (15 ml) of 3-chloromethylbenzoic acid 50.5 (1 g, 5.8 mmol) was heated at reflux, followed by the slow addition of N,N-dimethylformamide-di-t-butylacetal (5 m). The resulting solution was refluxed for 4 h, concentrated under reduced pressure and purified by silica gel column to afford 14.5 (0.8 g, 60 %).

25 **Aminopropyl-diethylphosphonate 14.6** is purchased from Acros

**Aminoethyl-diethylphosphonate oxalate 14.7** is purchased from Acros

30 **Aminopropyl-phenol-ethyl lactate phosphonate 15.5**

**N-CBZ-aminopropyl diphenylphosphonate 50.8:** An aqueous sodium hydroxide solution (50 mL of 1 N solution, 50 mmol) of 3-aminopropyl phosphonic acid 50.6 (3 g, 1.5 mmol)

was reacted with CBZ-Cl (4.1 g, 24 mmol) at room temperature overnight. The reaction mixture was washed with methylene chloride, acidified with Dowex 50wx8-200. The resin was filtered off. The filtrate was concentrated to dryness. The crude N-CBZ-aminopropyl phosphonic acid **50.7** (5.8 mmol) was suspended in CH<sub>3</sub>CN (40 mL), and reacted with  
5 thionyl chloride (5.2 g, 44 mmol) at reflux for 4 hr, concentrated, and azeotroped with CH<sub>3</sub>CN twice. The reaction mixture was redissolved in methylene chloride (20 mL), followed by the addition of phenol (3.2 g, 23 mmol), was cooled to 0°C. To this 0°C cold solution was added TEA (2.3 g, 23 mmol), and stirred at room temperature overnight. The reaction mixture was concentrated and purified on silica gel column chromatograph to afford  
10 **50.8** (1.5 g, 62 %).

**Monophenol derivative 50.9:** A CH<sub>3</sub>CN solution (5 mL) of **50.8** (0.8 g, 1.88 mmol) was cooled to 0°C, and treated with 1N NaOH aqueous solution (4 mL, 4 mmol) for 2 h. The reaction was diluted with water, extracted with ethyl acetate, acidified with Dowex 50wx8-  
15 200. The aqueous solution was concentrated to dryness to afford **50.9** (0.56 g, 86%).

**Monolactate derivative 50.10:** A DMF solution (1 mL) of crude **50.9** (0.17 g, 0.48 mmol), BOP reagent (0.43 g, 0.97 mmol), ethyl lactate (0.12 g, 1 mmol), and DIPEA (0.31 g, 2.4 mmol) was reacted for 4 hr at room temperature. The reaction mixture was partitioned  
20 between methylene chloride and 5 % citric acid aqueous solution. The organic solution was separated, concentrated, and purified on preparative TLC to give **50.10** (0.14 g, 66%).

**3-Aminopropyl lactate phosphonate 15.5:** An ethyl acetate/ethanol solution (10 mL/2 mL) of **50.10** (0.14 g, 0.31 mmol) was hydrogenated at 1 atm in the presence of 10% Pd/C (40  
25 mg) for 3 hr. The catalyst was filtered off. The filtrate was concentrated to dryness to afford **15.5** (0.14 g, quantitative). NMR (CDCl<sub>3</sub>): δ 8.0-8.2 (b, 3H), 7.1-7.4 (m, 5H), 4.9-5.0 (m, 1H), 4.15-4.3 (m, 2H), 3.1-3.35 (m, 2H), 2.1-2.4 (m, 4H), 1.4 (d, 3H), 1.3 (t, 3H).

**Aminopropyl-phenol-ethyl alanine phosphonate 15.6:** Compound **15.6** (80 mg) was  
30 prepared from the reaction of **50.9** (160 mg, 0.45 mmol) and L-alanine ethyl ester hydrochloride salt (0.11g, 0.68 mmol) in the presence of DIPEA and BOP reagent to give **50.11**, followed by the hydrogenation in the presence of 10% Pd/C and TFA to yield **15.6**. NMR (CDCl<sub>3</sub> + ~10 % CD<sub>3</sub>OD): δ 8.0-8.2 (b), 7.25-7.35 (t, 2H), 7.1-7.2 (m, 3H), 4.0-4.15

(m, 2H), 3.8-4.0 (m, 1H), 3.0-3.1 (m, 2H), 1.15-1.25 (m, 6H). P NMR ( $\text{CDCl}_3 + \sim 10\% \text{ CD}_3\text{OD}$ ): 32.1 & 32.4 ppm.

**Aminopropyl dibenzyl phosphonate 15.7 :**

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**N-BOC-3-aminopropyl phosphonic acid 50.13:** A THF-1N aqueous solution (16 mL-16 mL) of 3-aminopropyl phosphonic acid 50.12 (1 g, 7.2 mmol) was reacted with  $(\text{BOC})_2\text{O}$  (1.7 g, 7.9 mmol) overnight at room temperature. The reaction mixture was concentrated, and partitioned between methylene chloride and water. The aqueous solution was acidified with  
10 Dowex 50wx8-200. The resin was filtered off. The filtrate was concentrated to give **50.13** (2.2 g, 92 %).

**N-BOC-3-aminopropyl dibenzyl phosphonate 50.14:** A  $\text{CH}_3\text{CN}$  solution (10 mL) of **50.13** (0.15 g, 0.63 mmol), cesium carbonate (0.61 g, 1.88 mmol), and benzyl bromide (0.24 g, 1.57  
15 mmol) was heated at reflux overnight. The reaction mixture was cooled to room temperature, and diluted with methylene chloride. The white solid was filtered off, washed thoroughly with methylene chloride. The organic phase was concentrated, and purified on preparative TLC to give **50.14** (0.18 g, 70%). MS: 442 (M + Na).

**Aminopropyl dibenzyl phosphonate 15.7:** A methylene chloride solution (1.6 mL) of **50.14** (0.18 g) was treated with TFA (0.4 mL) for 1 hr. The reaction mixture was concentrated to dryness, and azeotroped with  $\text{CH}_3\text{CN}$  twice to afford **15.7** (0.2 g, as TFA salt). NMR  
20 ( $\text{CDCl}_3$ ):  $\delta$  8.6 (b, 2H), 7.9 (b, 2H), 7.2-7.4 (m, 10H), 4.71-5.0 (2 abq, 4H), 3.0 (b, 2H), 1.8-2 (m, 4H).  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ ): 32.0 ppm. F NMR ( $\text{CDCl}_3$ ): -76.5 ppm.

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**Aminomethyl diethylphosphonate 22.8** is purchased from Acros

**Bromomethyl, tetrahydropyran indazole 25.9** is prepared according to J. Org. Chem. 1997, 62, p5627

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Activity of the CCPPI Compounds

The enzyme inhibitory potency ( $K_i$ ), antiviral activity ( $\text{EC}_{50}$ ), and cytotoxicity ( $\text{CC}_{50}$ ) of the tested compounds were measured and demonstrated.

Biological assays used for the characterization of PI prodrugsHIV-1 Protease Enzyme Assay ( $K_i$ )

The assay is based on the fluorimetric detection of synthetic hexapeptide substrate cleavage

- 5 by HIV-1 protease in a defined reaction buffer as initially described by M.V.Toth and G.R.Marshall, Int. J. Peptide Protein Res. 36, 544 (1990)

*Substrate:* (2-aminobenzoyl)Thr-Ile-Nle-(p-nitro)Phe-Gln-Arg

Substrate supplied by Bachem California, Inc. (Torrance, CA; Cat. no. H-2992)

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*Enzyme:* recombinant HIV-1 protease expressed in E.Coli

Enzyme supplied by Bachem California, Inc. (Torrance, CA; Cat. no. H-9040)

*Reaction buffer:* 100 mM ammonium acetate, pH 5.3

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1 M sodium chloride

1 mM ethylenediaminetetraacetic acid

1 mM dithiothreitol

10% dimethylsulfoxide

20 *Assay protocol for the determination of inhibition constant  $K_i$ :*

1. Prepare series of solutions containing identical amount of the enzyme (1 to 2.5 nM) and a tested inhibitor at different concentrations in the reaction buffer
2. Transfer the solutions (190  $\mu$ L each) into a white 96-well plate
3. Preincubate for 15 min at 37°C
- 25 4. Solubilize the substrate in 100% dimethylsulfoxide at a concentration of 800  $\mu$ M. Start the reaction by adding 10  $\mu$ L of 800  $\mu$ M substrate into each well (final substrate concentration of 40  $\mu$ M)
5. Measure the real-time reaction kinetics at 37°C by using Gemini 96-well plate fluorimeter (Molecular Devices, Sunnyvale, CA) at  $\lambda(\text{Ex}) = 330$  nm and  $\lambda(\text{Em}) = 420$  nm
- 30 6. Determine initial velocities of the reactions with different inhibitor concentrations and calculate  $K_i$  (in picomolar concentration units) value by using EnzFitter program

(Biosoft, Cambridge, U.K.) according to an algorithm for tight-binding competitive inhibition described by Ermolieff J., Lin X., and Tang J., *Biochemistry* 36, 12364 (1997)

Anti-HIV-1 Cell Culture Assay ( $EC_{50}$ )

- 5 The assay is based on quantification of the HIV-1-associated cytopathic effect by a colorimetric detection of the viability of virus-infected cells in the presence or absence of tested inhibitors. The HIV-1-induced cell death is determined using a metabolic substrate 2,3-bis(2-methoxy-4-nitro-5-sulphophenyl)-2H-tetrazolium-5-carboxanilide (XTT) which is converted only by intact cells into a product with specific absorption characteristics as
- 10 described by Weislow OS, Kiser R, Fine DL, Bader J, Shoemaker RH and Boyd MR, *J. Natl. Cancer Inst.* 81, 577 (1989).

*Assay protocol for determination of  $EC_{50}$ :*

1. Maintain MT2 cells in RPMI-1640 medium supplemented with 5% fetal bovine serum  
15 and antibiotics.
2. Infect the cells with the wild-type HIV-1 strain IIIB (Advanced Biotechnologies, Columbia, MD) for 3 hours at 37°C using the virus inoculum corresponding to a multiplicity of infection equal to 0.01.
3. Prepare a set of solutions containing various concentrations of the tested inhibitor by  
20 making 5-fold serial dilutions in 96-well plate (100  $\mu$ L/well). Distribute the infected cells into the 96-well plate (20,000 cells in 100  $\mu$ L/well). Include samples with untreated infected and untreated mock-infected control cells.
4. Incubate the cells for 5 days at 37°C.
5. Prepare XTT solution (6 mL per assay plate) at a concentration of 2mg/mL in a  
25 phosphate-buffered saline pH 7.4. Heat the solution in water-bath for 5 min at 55°C. Add 50  $\mu$ L of N-methylphenazonium methasulfate (5  $\mu$ g/mL) per 6 mL of XTT solution.
6. Remove 100  $\mu$ L media from each well on the assay plate.
7. Add 100  $\mu$ L of the XTT substrate solution per well and incubate at 37°C for 45 to 60 min in a CO<sub>2</sub> incubator.
- 30 8. Add 20  $\mu$ L of 2% Triton X-100 per well to inactivate the virus.
9. Read the absorbance at 450 nm with subtracting off the background absorbance at 650 nm.

10. Plot the percentage absorbance relative to untreated control and estimate the  $EC_{50}$  value as drug concentration resulting in a 50% protection of the infected cells.

Cytotoxicity Cell Culture Assay ( $CC_{50}$ ):

- 5 The assay is based on the evaluation of cytotoxic effect of tested compounds using a metabolic substrate 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT) as described by Weislow OS, Kiser R, Fine DL, Bader J, Shoemaker RH and Boyd MR, J. Natl. Cancer Inst. 81, 577 (1989).
- 10 *Assay protocol for determination of  $CC_{50}$ :*
1. Maintain MT-2 cells in RPMI-1640 medium supplemented with 5% fetal bovine serum and antibiotics.
  2. Prepare a set of solutions containing various concentrations of the tested inhibitor by making 5-fold serial dilutions in 96-well plate (100  $\mu$ L /well). Distribute cells into the
  - 15 96-well plate (20,000 cells in 100  $\mu$ L/well). Include samples with untreated cells as a control.
  3. Incubate the cells for 5 days at 37°C.
  4. Prepare XTT solution (6 mL per assay plate) in dark at a concentration of 2mg/mL in a phosphate-buffered saline pH 7.4. Heat the solution in a water-bath at 55°C for 5 min.
  - 20 Add 50  $\mu$ L of N-methylphenazonium methasulfate (5  $\mu$ g/mL) per 6 mL of XTT solution.
  5. Remove 100  $\mu$ L media from each well on the assay plate and add 100  $\mu$ L of the XTT substrate solution per well. Incubate at 37°C for 45 to 60 min in a CO<sub>2</sub> incubator.
  6. Add 20  $\mu$ L of 2% Triton X-100 per well to stop the metabolic conversion of XTT.
  7. Read the absorbance at 450 nm with subtracting off the background at 650 nm.
  - 25 8. Plot the percentage absorbance relative to untreated control and estimate the  $CC_{50}$  value as drug concentration resulting in a 50% inhibition of the cell growth. Consider the absorbance being directly proportional to the cell growth.

30 Resistance Evaluation ( $I50V$  and  $I84V/L90M$  fold change)

The assay is based on the determination of a difference in the susceptibility to a particular HIV protease inhibitor between the wild-type HIV-1 strain and a mutant HIV-1 strain

containing specific drug resistance-associated mutation(s) in the viral protease gene. The absolute susceptibility of each virus ( $EC_{50}$ ) to a particular tested compound is measured by using the XTF-based cytopathic assay as described above. The degree of resistance to a tested compound is calculated as fold difference in  $EC_{50}$  between the wild type and a specific mutant virus. This represents a standard approach for HIV drug resistance evaluation as documented in various publications (e.g. Maguire et al., *Antimicrob. Agents Chemother.* 46: 731, 2002; Gong et al., *Antimicrob. Agents Chemother.* 44: 2319, 2000; Vandamme and De Clercq, in *Antiviral Therapy* (Ed. E. De Clercq), pp. 243, ASM Press, Washington, DC, 2001).

HIV-1 strains used for the resistance evaluation:

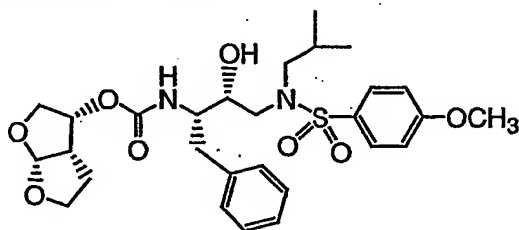
Two strains of mutant viruses containing I50V mutation in the protease gene have been used in the resistance assays: one with M46I/I47V/I50V mutations (designated I50V #1) and the other with L10I/M46I/I50V (designated I50V #2) mutations in the viral protease gene. A third virus with I84V/L90M mutations was also employed in the resistance assays. Mutants I50V #1 and I84V/L90M were constructed by a homologous recombination between three overlapping DNA fragments: 1. linearized plasmid containing wild-type HIV-1 proviral DNA (strain HXB2D) with the protease and reverse transcriptase genes deleted, 2. DNA fragment generated by PCR amplification containing reverse transcriptase gene from HXB2D strain (wild-type), 3. DNA fragment of mutated viral protease gene that has been generated by PCR amplification. An approach similar to that described by Shi and Mellors in *Antimicrob. Agents Chemother.* 41: 2781-85, 1997 was used for the construction of mutant viruses from the generated DNA fragments. Mixture of DNA fragments was delivered into Sup-T1 cells by using a standard electroporation technique. The cells were cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum and antibiotics until the recombinant virus emerged (usually 10 to 15 days following the electroporation). Cell culture supernatant containing the recombinant virus was harvested and stored in aliquots. After verification of protease gene sequence and determination of the infectious virus titer, the viral stock was used for drug resistance studies. Mutant I50V #2 is an amprenavir-resistant HIV-1 strain selected *in vitro* from the wild-type IIIB strain in the presence of increasing concentration of amprenavir over a period of > 9 months using an approach similar to that described by Partaledis et al., *J. Virol.* 69: 5228-5235, 1995. Virus capable of growing in the presence of 5



$\mu$ M amprenavir was harvested from the supernatant of infected cells and used for resistance assays following the titration and protease gene sequencing.

Example 37: Activity of the Tested Compounds

- 5 The enzyme inhibitory potency ( $K_i$ ), antiviral activity ( $EC_{50}$ ), and cytotoxicity ( $CC_{50}$ ) of the tested compounds are summarized in Table 1.



94-003

**Table 1: Enzyme inhibition activity (Ki), antiviral cell culture activity (EC50), and cytotoxicity (CC50) of the tested compounds.**

Substitution of (P1)phenyl	Compound	Phosphonate substitution	HIV-1 protease inhibition Ki [pM]	Anti-HIV-1 Cell Culture Activity EC50 [nM]	Cytotoxicity CC50 [ $\mu$ M]
none	Amprenavir	none	45.6 $\pm$ 18.2	16 $\pm$ 2.2	
none	94-003	none	1.46 $\pm$ 0.58	1.4 $\pm$ 0.3	
phosphonyl	27	diacid	11.8 $\pm$ 6.0	> 100,000	> 100
	28	diethyl	1.2 $\pm$ 0.8	5.0 $\pm$ 2.8	70
phosphonyl methoxy	11	diacid	2.1 $\pm$ 0.2	4,800 $\pm$ 1,800	> 100
	13	diethyl	2.6 $\pm$ 1.5	3.0 $\pm$ 0	50
	14	dibenzyl	12.7 $\pm$ 1.9	2.3 $\pm$ 0.4	35
	16c	bis(Ala-ethylester)	15.4 $\pm$ 0.85	105 $\pm$ 43	60
	16d	bis(Ala-butylester)	18.75 $\pm$ 3.04	6.0 $\pm$ 1.4	
	16e	bis(ABA-ethylester)	8.8 $\pm$ 1.7	12.5 $\pm$ 3.5	
	16f	bis(ABA-butylester)	3.5 $\pm$ 1.4	4.8 $\pm$ 1.8	
	16a	bis(Gly-ethylester)	29 $\pm$ 8.2	330 $\pm$ 230	
	16b	bis(Gly-butylester)	4.9 $\pm$ 1.8	17.5 $\pm$ 10.5	
	16g	bis(Leu-ethylester)	29 $\pm$ 9	6.8 $\pm$ 0.4	
	16h	bis(Leu-butylester)	31.7 $\pm$ 19.3	120 $\pm$ 42	
	16i	bis(Phe-ethylester)		17 $\pm$ 12	
	16j	bis(Phe-butylester)		35 $\pm$ 7	
	15	bis(POC)	36	825 $\pm$ 106	
	11	Monoethyl, monoacid	0.45 $\pm$ 0.15	700 $\pm$ 0	

## 5 Cross-Resistance Profile Assay

The assay is based on the determination of a difference in the susceptibility to a particular HIV protease inhibitor between the wild-type HIV-1 strain and a recombinant HIV-1 strain expressing specific drug resistance-associated mutation(s) in the viral protease gene. The absolute susceptibility of each virus to a particular tested compound is measured by using the XTT-based cytopathic assay as described in Example B. The degree of resistance to a tested compound is calculated as fold difference in EC50 between the wild type and a specific mutant virus.

Recombinant HIV-1 strains with resistance mutations in the protease gene:

- One mutant virus (82T/84V) was obtained from NIH AIDS Research and Reference Reagent Program (Rockville, MD). Majority of the mutant HIV-1 strains were constructed by a homologous recombination between three overlapping DNA fragments: 1. linearized plasmid containing wild-type HIV-1 proviral DNA (strain HXB2D) with the protease and reverse transcriptase genes deleted, 2. DNA fragment generated by PCR amplification containing reverse transcriptase gene from HXB2D strain (wild-type), 3. DNA fragment generated by RT-PCR amplification from patients plasma samples containing viral protease gene with specific mutations selected during antiretroviral therapy with various protease inhibitors.
- Additional mutant HIV-1 strains were constructed by a modified procedure relying on a homologous recombination of only two overlapping DNA fragments: 1. linearized plasmid containing wild-type HIV-1 proviral DNA (strain HXB2D) with only the protease gene deleted, and 2. DNA fragment generated by RT-PCR amplification from patients plasma samples containing viral protease gene with specific mutations. In both cases, mixture of DNA fragments was delivered into Sup-T1 cells by using a standard electroporation technique. The cells were cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum and antibiotics until the recombinant virus emerged (usually 10 to 15 days following the electroporation). Cell culture supernatant containing the recombinant virus was harvested and stored in aliquots. After determination of the virus titer the virus stock was used for drug resistance studies.

Example 39: Cross-Resistance Profile of the Tested Compounds

Cross-resistance profile of currently used HIV-1 protease inhibitors was compared with that of the newly invented compounds (Table 2).

Table 2. Cross-resistance profile of HIV-1 protease inhibitors

Compound	EC 50 [nM]	Fold Change in EC <sub>50</sub> Relative to WT HIV-1											Total No. of Resis- tant Viruses <sup>b</sup>
		8K <sup>a</sup> 46I 90M	46I 84A	10I 48V 54V 82A	46I 47V 50V	10R 46I 82T 84V	30N 50S 82I 88D	54V 71V 82S	10F 46I 71V 82T 90M	10I 48V 71V 82A 90M	48V 54V 71V 82S	10I 84V 71V 73S 90M	
Amprenavir	20	1.25	14	2	38	4	0.8	4	13	2.5	2	10	4
Nelfinavir	14	13	11	11.5	2	3	43	12	33	27	12	65	9
Indinavir	15	4	10	15	nd	7	1	10	13	28	23	43	8
Ritonavir	15	34	18	20	13	47	2	20	32	22	>50	42	10
Saquinavir	4	1	2.5	11	1	2.5	1	3	2.5	12	45	40	4
Lopinavir	8	nd	9	nd	19	11	nd	nd	7.5	4.5	60	11	6
Tipranavir	80	nd	1	0.4	0.5	5	0.5	3.5	3	0.3	2	nd	1
94-003	0.5	nd	8	0.5	29	nd	0.4	3.5	nd	nd	nd	8	3
GS 16503	16	1.2	1	0.4	3.3	1	0.6	0.9	1	0.4	0.5	2	0
GS 16571	22	1.8	1	0.3	0.8	0.6	0.7	0.6	0.8	0.2	0.2	0.9	0
GS 16587	15	1.5	1	0.5	2	1	1	0.9	1	0.4	0.4	1	0

5 <sup>a</sup> Resistance-associated mutations present in the viral protease. The highlighted changes represent primary resistance mutations.

<sup>b</sup> Resistance is considered as a 5-fold and higher change in the EC<sub>50</sub> value of the mutant virus relative to the wild-type virus.

### Example Section N

#### Plasma and PBMC Exposure Following Intravenous and Oral Administration of Prodrug to Beagle Dogs

The pharmacokinetics of a phosphonate prodrug GS77366 (P1-monoLac-iPr), its active metabolite (metabolite X, or GS77568), and GS8373 were studied in dogs following intravenous and oral administration of the prodrug.

Dose Administration and Sample Collection. The in-life phase of this study was conducted in accordance with the USDA Animal Welfare Act and the Public Health Service Policy on Humane Care and Use of Laboratory Animals, and followed the standards for animal husbandry and care found in the Guide for the Care and Use of Laboratory Animals, 7<sup>th</sup>

Edition, Revised 1996. All animal housing and study procedures involving live animals were carried out at a facility which had been accredited by the Association for Assessment and Accreditation of Laboratory Animal Care - International (AAALAC).

Each animal in a group of 4 female beagle dogs was given a bolus dose of GS77366 (P1-monoLac-iPr) intravenously at 1 mg/kg in a formulation containing 40% PEG 300, 20% propylene glycol and 40% of 5% dextrose. Another group of 4 female beagle dogs was dosed with GS77366 via oral gavage at 20 mg/kg in a formulation containing 60% Vitamin-E TPGS, 30% PEG 400 and 10% propylene glycol.

Blood samples were collected pre-dose, and at 5 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, 8 hr, 12 hr and 24 hr post-dose. Plasma (0.5 to 1 mL) was prepared from each sample and kept at -70°C until analysis. Blood samples (8 mL) were also collected from each dog at 2, 8 and 24 hr post dose in Becton-Dickinson CPT vacutainer tubes. PBMCs were isolated from the blood by centrifugation for 15 minutes at 1500 to 1800 G. After centrifugation, the fraction containing PBMCs was transferred to a 15 mL conical centrifuge tube and the PBMCs were washed twice with phosphate buffered saline (PBS) without Ca<sup>2+</sup> and Mg<sup>2+</sup>. The final wash of the cell pellet was kept at -70°C until analysis.

Measurement of the prodrug, metabolite X and GS8373 in plasma and PBMCs. For plasma sample analysis, the samples were processed by a solid phase extraction (SPE) procedure outlined below. Speedisk C18 solid phase extraction cartridges (1 mL, 20 mg, 10 µM, from

J.T. Baker) were conditioned with 200  $\mu$ L of methanol followed by 200  $\mu$ L of water. An aliquot of 200  $\mu$ L of plasma sample was applied to each cartridge, followed by two washing steps each with 200  $\mu$ L of deionized water. The compounds were eluted from the cartridges with a two-step process each with 125  $\mu$ L of methanol. Each well was added 50  $\mu$ L of water and mixed. An aliquot of 25  $\mu$ L of the mixture was injected onto a ThermoFinnigan TSQ Quantum LC/MS/MS system.

The column used in liquid chromatography was HyPURITY® C18 (50 x 2.1 mm, 3.5  $\mu$ m) from Thermo-Hypersil. Mobile phase A contained 10% acetonitrile in 10 mM ammonium formate, pH 3.0. Mobile phase B contained 90% acetonitrile in 10 mM ammonium formate, pH 4.6. The chromatography was carried out at a flow rate of 250  $\mu$ L/min under an isocratic condition of 40% mobile phase A and 60% mobile phase B. Selected reaction monitoring (SRM) were used to measure GS77366, GS8373 and Metabolite X with the positive ionization mode on the electrospray probe. The limit of quantitation (LOQ) was 1 nM for GS77366, GS8373 and GS77568 (Metabolite X) in plasma.

For PBMC sample analysis, phosphate buffered saline (PBS) was added to each PBMC pellet to bring the total sample volume to 500  $\mu$ L in each sample. An aliquot of 150  $\mu$ L from each PBMC sample was mixed with an equal volume of methanol, followed by the addition of 700  $\mu$ L of 1% formic acid in water. The resulting mixture was applied to a Speedisk C18 solid phase extraction cartridge (1 mL, 20 mg, 10  $\mu$ m, from J.T. Baker) which had been conditioned as described above. The compounds were eluted with methanol after washing the cartridge 3 times with 10% methanol. The solvent was evaporated under a stream of N<sub>2</sub> and the sample was reconstituted in 150  $\mu$ L of 30% methanol. An aliquot of 75  $\mu$ L of the solution was injected for LC/MS/MS analysis. The limit of quantitation was 0.1 ng/mL in the PBMC suspension.

Pharmacokinetic Calculations. The pharmacokinetic parameters were calculated using WinNonlin. Noncompartmental analysis was used for all pharmacokinetic calculation. The intracellular concentrations in PBMCs were calculated from the measured concentrations in PBMC suspension on the basis of a reported volume of 0.2 picoliter/cell (B.L. Robins, R.V. Srinivas, C.Kim, N.Bischofberger, and A.Fridland, (1998) Antimicrob. Agents Chemother. 42, 612).

Plasma and PBMC Concentration-time Profiles.

The concentration-time profiles of GS77366, GS77568 and GS8373 in plasma and PBMCs following intravenous dosing of GS77366 were compared at 1 mg/kg in dogs. The data demonstrate that the prodrug can effectively deliver the active components (metabolite X and GS8373) into cells that are primarily responsible for HIV replication, and that the active components in these cells had much longer half-life than in plasma.

The pharmacokinetic properties of GS77568 in PBMCs following oral administration of GS77366 in dogs are compared with that of nelfinavir and amprenavir, two marketed HIV protease inhibitors (Table 3). These data show that the active component (GS77568) from the phosphonate prodrug had sustained levels in PBMCs compared to nelfinavir and amprenavir.

**Table 3. Comparison of GS77568 with nelfinavir and amprenavir in PBMCs following oral administration in beagle dogs.**

Compound	Dose	t <sub>1/2</sub> (hr)	AUC <sub>(2-24 hr)</sub>
Nelfinavir	17.5 mg/kg	3.0 hr	33,000 nM·hr
Amprenavir	20 mg/kg	1.7 hr	102,000 nM·hr
GS77568	20 mg/kg of GS77366	> 20 hr	42,200 nM·hr

**Example Section O****Intracellular Metabolism/In Vitro Stability**

## 5 1. Uptake and Persistence in MT2 cells, quiescent and stimulated PBMC

The protease inhibitor (PI) phosphonate prodrugs undergo rapid cell uptake and metabolism to produce acid metabolites including the parent phosphonic acid. Due to the presence of charges, the acid metabolites are significantly more persistent in the cells than non-charged PI's. In order to estimate the relative intracellular levels of the different PI prodrugs, three  
10 compounds representative of three classes of phosphonate PI prodrugs – bisamidate phosphonate, monoamidate phenoxy phosphonate and monolactate phenoxy phosphonate (Figure 1) were incubated at 10  $\mu$ M for 1 hr with MT-2 cells, stimulated and quiescent peripheral blood mononuclear cells (PBMC) (pulse phase). After incubation, the cells were washed, resuspended in the cell culture media and incubated for 24 hr (chase phase). At  
15 specific time points, the cells were washed, lysed and the lysates were analyzed by HPLC with UV detection. Typically, the cell lysates were centrifuged and 100  $\mu$ L of the supernatant were mixed with 200  $\mu$ L of 7.5  $\mu$ M amprenavir (Internal Standard) in 80% acetonitrile/20% water and injected into an HPLC system (70  $\mu$ L).

20 **HPLC Conditions:**

Analytical Column: Prodigy ODS-3, 75 x 4.6, 3 $\mu$  + C18 guard at 40°C

Gradient:

Mobile Phase A: 20 mM ammonium acetate in 10% ACN/90% H<sub>2</sub>O

Mobile Phase B: 20 mM ammonium acetate in 70% ACN/30% H<sub>2</sub>O

25 30-100%B in 4 min, 100%B for 2 min, 30%B for 2 min at 2.5 mL/min.

Run Time: 8 min

UV Detection at 245 nm

Concentrations of Intracellular metabolites were calculated based on cell volume 0.2  $\mu$ L/mLn  
30 cells for PBMC and 0.338  $\mu$ L / mLn (0.676  $\mu$ L / mL) for MT-2 cells.

Chemical Structures of Selected Protease Inhibitor Phosphonate Prodrugs and Intracellular Metabolites:



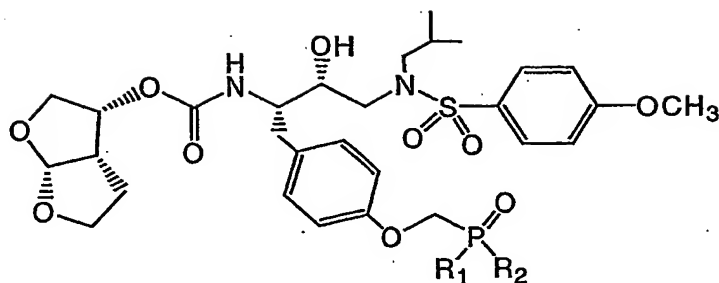


Table 4:

GS No.	R1	R2	EC <sub>50</sub> (nM)
8373	OH	OH	4,800±1,800
16503	HNCH(CH <sub>3</sub> )COOBu	HNCH(CH <sub>3</sub> )COOBu	6.0±1.4
16571	OPh	HNCH(CH <sub>3</sub> )COOEt	15±5
17394	OPh	OCH(CH <sub>3</sub> )COOEt	20±7
16576	OPh	HNCH(CH <sub>2</sub> CH <sub>3</sub> )COOEt	12.6±4.8
Met X	OH	HNCH(CH <sub>3</sub> )COOH	>10,000
Met LX	OH	OCH(CH <sub>3</sub> )COOEt	1750±354

- 5 A significant uptake and conversion of all 3 compounds in all cell types was observed (Table 4). The uptake in the quiescent PBMC was 2-3-fold greater than in the stimulated cells. GS-16503 and GS-16571 were metabolized to Metabolite X and GS-8373. GS-17394 metabolized to the Metabolite LX. Apparent intracellular half-lives were similar for all metabolites in all cell types (7-12 hr). A persistence of Total Acid Metabolites of Protease Inhibitor Prodrugs in Stimulated (A), Quiescent PBMC (B) and MT-2 Cells (C) (1 hr, 10  $\mu$ M Pulse, 24 hr Chase) was observed.

## 2. Uptake and Persistence in Stimulated and Quiescent T-cells

- 15 Since HIV mainly targets T-lymphocytes, it is important to establish the uptake, metabolism and persistence of the metabolites in the human T-cells. In order to estimate the relative intracellular levels of the different PI prodrugs, GS-16503, 16571 and 17394 were incubated at 10  $\mu$ M for 1 hr with quiescent and stimulated T-cells (pulse phase). The prodrugs were compared with a non-prodrug PI, nelfinavir. After incubation, the cells were washed, resuspended in the cell culture media and incubated for 4 hr (chase phase). At specific time

points, the cells were washed, lysed and the lysates were analyzed by HPLC with UV detection. The sample preparation and analysis were similar to the ones described for MT-2 cells, quiescent and stimulated PBMC.

- 5 Table 5 demonstrate the levels of total acid metabolites and corresponding prodrugs in T-cells following pulse/chase and continuous incubation. There was significant cell uptake/metabolism in T-lymphocytes. There was no apparent difference in uptake between stimulated and quiescent T-lymphocytes. There was significantly higher uptake of phosphonate PI's than nelfinavir. GS17394 demonstrates higher intracellular levels than
- 10 GS16571 and GS16503. The degree of conversion to acid metabolites varied between different prodrugs. GS-17394 demonstrated the highest degree of conversion, followed by GS-16503 and GS-16571. The metabolites, generally, were an equal mixture of the mono-phosphonic acid metabolite and GS-8373 except for GS-17394, where Metabolite LX was stable, with no GS-8373 formed.

15

**Table 5. Intracellular Levels of Metabolites and Intact Prodrug Following Continuous and 1 hr Pulse/4 hr Chase Incubation (10  $\mu$ M/0.7 mLn cells/1 mL) of 10  $\mu$ M PI Prodrugs and Nelfinavir with Quiescent and Stimulated T-cell**

Compound	Time (h)	Continuous Incubation				1 hr Pulse /4 hr Chase			
		Quiescent T-cells		Stimulated T-cells		Quiescent T-cells		Stimulated T-cells	
		Acid Met ( $\mu$ M)	Prodrug ( $\mu$ M)	Acid Met ( $\mu$ M)	Prodrug ( $\mu$ M)	Acid Met ( $\mu$ M)	Prodrug ( $\mu$ M)	Acid Met ( $\mu$ M)	Prodrug ( $\mu$ M)
16503	0	1180	42	2278	0	2989	40	1323	139
	2	3170	88	1083	116	1867	4	1137	31
	4	5262	0	3198	31	1054	119	1008	0
16571	0	388	1392	187	1417	1042	181	858	218
	2	947	841	1895	807	1170	82	1006	35
	4	3518	464	6147	474	1176	37	616	25
17394	0	948	1155	186	1194	4480	14	2818	10
	2	7231	413	3748	471	2898	33	1083	51
	4	10153	167	3867	228	1548	39	943	104
Nelfinavir	0		101		86		886		1239
	2		856		846		725		770
	4		992		1526		171		544

20

### 3. PBMC Uptake and Metabolism of Selected PI Prodrugs Following 1-hr Incubation in MT-2 Cells at 10, 5 and 1 $\mu$ M.

To were similar to the determine if the cell uptake/metabolism is concentration dependent, selected PI's were incubated with the 1 mL of MT-2 cell suspension (2.74 mLn cells/mL) for 1 hr at 37°C at 3 different concentrations: 10, 5 and 1  $\mu$ M. Following incubation, cells were washed twice with the cell culture medium, lysed and assayed using HPLC with UV detection. The sample preparation and analysis ones described for MT-2 cells, quiescent and stimulated PBMC. Intracellular concentrations were calculated based on cell count, a published single cell volume of 0.338 pL for MT-2 cells, and concentrations of analytes in cell lysates. Data are shown in Table 6.

Uptake of all three selected PI's in MT-2 cells appears to be concentration-independent in the 1-10  $\mu$ M range. Metabolism (conversion to acid metabolites) appeared to be concentration-dependent for GS-16503 and GS-16577 (3-fold increase at 1  $\mu$ M vs. 10  $\mu$ M) but independent for GS-17394 (monolactate). Conversion from a respective metabolite X to GS-8373 was concentration-independent for both GS-16503 and GS-16577 (no conversion was observed for metabolite LX of GS-17394).

**Table 6. Uptake and Metabolism of Selected PI Prodrugs Following 1-hr Incubation in MT-2 Cells at 10, 5 and 1  $\mu$ M.**

Compound	Extracellular Concentration, $\mu$ M	Cell-Associated Prodrug and Metabolites Concentration, $\mu$ M				% Conversion to acid metabolites
		Metabolite X	GS8373	Prodrug	Total	
GS-17394	10	1358	0	635	1993	68
	5	916	0	449	1365	67
	1	196	0	63	260	76
GS-16576	10	478	238	2519	3235	22
	5	250	148	621	1043	40
	1	65	36	61	168	64
GS-16503	10	120	86	1506	1712	12
	5	58	60	579	697	17
	1	12	18	74	104	29

\* For GS16576, Metabolite X is mono-aminobutyric acid

**4. PBMC Uptake and Metabolism of Selected PI Prodrugs Following 1-hr Incubation in Human Whole Blood at 10  $\mu$ M.**

5

In order to estimate the relative intracellular levels of the different PI prodrugs under conditions simulating the in vivo environment, compounds representative of three classes of phosphonate PI prodrugs – bisamidate phosphonate (GS-16503), monoamidate phenoxy phosphonate (GS-16571) and monolactate phenoxy phosphonate (GS-17394) were incubated at 10  $\mu$ M for 1 hr with intact human whole blood at 37°C. After incubation, PBMC were isolated, then lysed and the lysates were analyzed by HPLC with UV detection. The results of analysis are shown in Table 7. There was significant cell uptake/metabolism following incubation in whole blood. There was no apparent difference in uptake between GS-16503 and GS-16571. GS-17394 demonstrated significantly higher intracellular levels than GS-16571 and GS-16503.

15

The degree of conversion to acid metabolites varies between different prodrugs after 1 hr incubation. GS-17394 demonstrated the highest degree of conversion, followed by GS-16503 and GS-16571 (Table 7). The metabolites, generally, were an equimolar mixture of the mono-phosphonic acid metabolite and GS-8373 (parent acid) except for GS-17394, where Metabolite LX was stable with no GS-8373 formed.

20

**Table 7. PBMC Uptake and Metabolism of Selected PI Prodrugs Following 1-hr Incubation in Human Whole Blood at 10  $\mu$ M (Mean  $\pm$  SD, N=3).**

25

GS#	Intracellular Prodrug and Metabolites Concentration, $\mu$ M			Major Intracellular Metabolites
	Acid Metabolite	Prodrug, $\mu$ M	Total, $\mu$ M	
16503	279 $\pm$ 47	61 $\pm$ 40	340 $\pm$ 35	X, GS-8373
16571	319 $\pm$ 112	137 $\pm$ 62	432 $\pm$ 208	X, GS-8373
17394	629 $\pm$ 303	69 $\pm$ 85	698 $\pm$ 301	LX

\* PBMC Intracellular Volume = 0.2  $\mu$ L/mln

#### 5. Distribution of PI Prodrugs in PBMC

5 In order to compare distribution and persistence of PI phosphonate prodrugs with those of non-prodrug PI's, GS-16503, GS-17394 and nelfinavir, were incubated at 10  $\mu$ M for 1 hr with PBMC (pulse phase). After incubation, the cells were washed, resuspended in the cell culture media and incubated for 20 more hr (chase phase). At specific time points, the cells were washed and lysed. The cell cytosol was separated from membranes by centrifugation at 9000  
10 xg. Both cytosol and membranes were extracted with acetonitrile and analyzed by HPLC with UV detection.

Table 8 shows the levels of total acid metabolites and corresponding prodrugs in the cytosol and membranes before and after the 22 hr chase. Both prodrugs exhibited complete  
15 conversion to the acid metabolites (GS-8373 and X for GS-16503 and LX for GS-17394, respectively). The levels of the acid metabolites of the PI phosphonate prodrugs in the cytosol fraction were 2-3-fold greater than those in the membrane fraction after the 1 hr pulse and 10-fold greater after the 22 hr chase. Nelfinavir was present only in the membrane fractions. The uptake of GS-17394 was about 3-fold greater than that of GS-16503 and 30-  
20 fold greater than nelfinavir. The metabolites were an equimolar mixture of metabolite X and GS-8373 (parent acid) for GS-16503 and only metabolite LX for GS-17394.

**Table 8. Uptake and Cell Distribution of Metabolites and Intact Prodrugs Following Continuous and 1 hr Pulse/22 hr Chase Incubation of 10  $\mu$ M PI Prodrugs and Nelfinavir with Quiescent PBMC.**

GS#	Cell Type	Fraction	Cell-Associated PI, pmol/mln cells			
			1 hr Pulse/ 0 hr Chase		1 hr Pulse/ 22 hr Chase	
			Acid Metabolites	Prodrug	Acid Metabolites	Prodrug
GS-16503	PBMC	Membrane	228	0	9	0
GS-16503	PBMC	Cytosol	390	0	130	0
GS-17394	PBMC	Membrane	335	0	26	0
GS-17394	PBMC	Cytosol	894	0	249	0
Nelfinavir	PBMC	Membrane		42		25
Nelfinavir	PBMC	Cytosol		0		0

Uptake and cell distribution of metabolites and intact prodrugs following 1 hr pulse/22 hr chase incubation of 10  $\mu$ M PI prodrugs and Nelfinavir with quiescent PBMC were measured.

#### 6. PBMC Extract/Dog Plasma/Human Serum Stability of Selected PI Prodrugs

The *in vitro* metabolism and stability of the PI phosphonate prodrugs were determined in PBMC extract, dog plasma and human serum (Table 9). Biological samples listed below (120  $\mu$ L) were transferred into an 8-tube strip placed in the aluminum 37°C heating block/holder and incubated at 37°C for 5 min. Aliquots (2.5  $\mu$ L) of solution containing 1 mM of test compounds in DMSO, were transferred to a clean 8-tube strip, placed in the aluminum 37°C heating block/holder. 60  $\mu$ L aliquots of 80% acetonitrile/20% water containing 7.5  $\mu$ M of amprenavir as an internal standard for HPLC analysis were placed into five 8-tube strips and kept on ice/refrigerated prior to use. An enzymatic reaction was started by adding 120  $\mu$ L aliquots of a biological sample to the strip with the test compounds using a multichannel pipet. The strip was immediately vortex-mixed and the reaction mixture (20  $\mu$ L) was sampled and transferred to the Internal Standard/ACN strip. The sample was considered the time-zero sample (actual time was 1-2 min). Then, at specific time points, the

reaction mixture (20  $\mu$ L) was sampled and transferred to the corresponding IS/ACN strip. Typical sampling times were 6, 20, 60 and 120 min. When all time points were sampled, an 80  $\mu$ L aliquot of water was added to each tube and strips were centrifuged for 30 min at 3000xG. The supernatants were analyzed with HPLC under the following conditions:

5

Column: Inertsil ODS-3, 75 x 4.6 mm, 3  $\mu$ m at 40°C.

Mobile Phase A: 20 mM ammonium acetate in 10%ACN/90%water

Mobile Phase B 20 mM ammonium acetate in 70%ACN/30%water

Gradient: 20% B to 100% B in 4 min, 2 min 100% B, 2 min 20% B

10 Flow Rate: 2 mL/min

Detection: UV at 243 nm

Run Time: 8 min

The biological samples evaluated were as follows:

- 15 PBMC cell extract was prepared from fresh cells using a modified published procedure (A. Pompon, I. Lefebvre, J-L. Imbach, S. Kahn, and D. Farquhar, Antiviral Chemistry & Chemotherapy, 5, 91 - 98 (1994)). Briefly, the extract was prepared as following: The cells were separated from their culture medium by centrifugation (1000 g, 15 min, ambient temperature). The residue (about 100  $\mu$ L,  $3.5 \times 10^8$  cells) was resuspended in 4 mL of a
- 20 buffer (0.010 M HEPES, pH 7.4, 50 mM potassium chloride, 5 mM magnesium chloride and 5 mM dl-dithiothreitol) and sonicated. The lysate was centrifuged (9000 g, 10 min, 4°C) to remove membranes. The upper layer (0.5 mg protein/mL) was stored at -70°C. The reaction mixture contained the cell extract at about 0.5 mg protein/mL.

Human serum (pooled normal human serum from George King Biomedical Systems, Inc.).

- 25 Protein concentration in the reaction mixture was about 60 mg protein/mL.

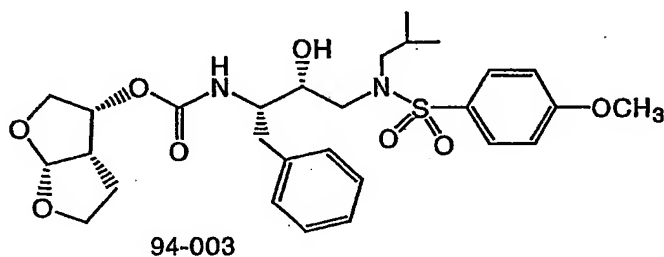
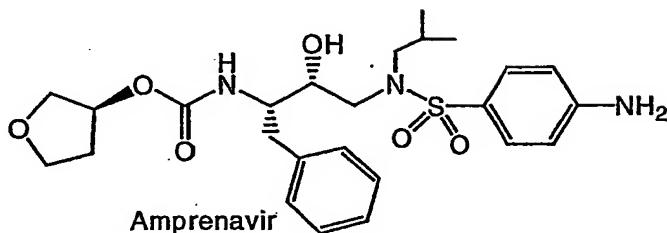
Dog Plasma (pooled normal dog plasma (EDTA) from Pel Freez, Inc.). Protein concentration in the reaction mixture was about 60 mg protein/mL.

**Table 9: PBMC Extract/Dog Plasma/Human Serum Stability of Selected PI Prodrugs**

GS#	PBMC Extract <sup>1</sup> T <sub>1/2</sub> , min	Dog Plasma T <sub>1/2</sub> , min	Human Serum T <sub>1/2</sub> , min	HIV EC <sub>50</sub> (nM)
16503	2	368	>>400	6.0 ± 1.4
16571	49	126	110	15 ± 5
17394	15	144	49	20 ± 7

5

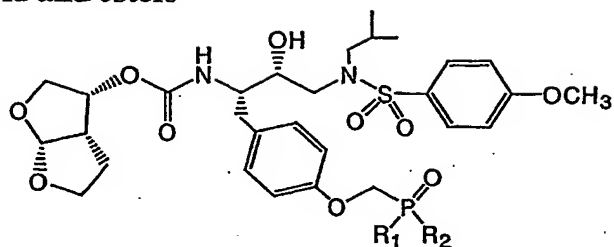


**Example Section P****Table 10: Enzymatic and Cellular data****Formula II ALPPI activity**

10	<u>Ki [pM]</u>	
	≤ 10	+++
	> 10 to ≤ 100	++
	> 100 to ≤ 1,000	+
	> 1,000	-
15	<u>EC<sub>50</sub> [nM]</u>	
	≤ 50	+++
	> 50 to ≤ 500	++
	> 500 to ≤ 5,000	+
	> 5,000	-
20	<u>I50V and I84V/L90M fold change</u>	
	> 30	+++
	> 10 to ≤ 30	++
	> 3 to ≤ 10	+
	≤ 3	-
25	<u>CC<sub>50</sub> [μM]</u>	
	≤ 5	++
	> 5 to ≤ 50	+
	> 50	-
30		

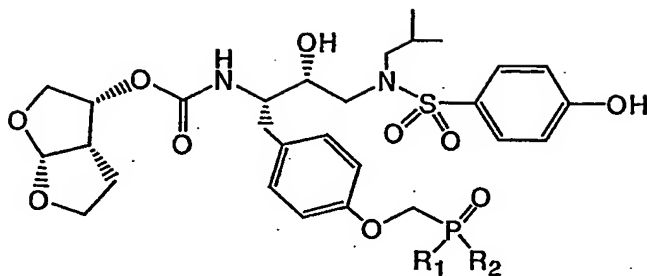
Compound	Ki (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I50V (#2) fold change	I84V/L90 M fold change	CC <sub>50</sub> (μM)
Saquinavir	++	+++	—	—	+++	
Nelfinavir	+	+++	—	+	+++	
Indinavir	+	+++	—	+	+++	
Ritonavir	++	+++	++	++	+++	
Lopinavir	++	+++	++	+++	++	
Amprenavir	+	+++	+++	+++	++	—
Atazanavir	++	+++	—	—	+++	
Tipranavir	++	++	—	—	+	
94-003	+++	+++	+++	+++	++	+
TMC114	+++	+++	++	++	—	

## P1-Phosphonic acid and esters



R1	R2	Ki (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> (μM)
OH	OH	+++	+	-	-	-
OMe	OMe	++	+++			
OEt	OEt	+++	+++	-	-	+
OCH <sub>2</sub> CF <sub>3</sub>	OCH <sub>2</sub> CF <sub>3</sub>	++	-			
OiPr	OiPr	++	+++	-	-	
OPh	OPh		+++			
OMe	OPh	++	+++			
OEt	OPh	+++	+++			
OBn	OBn	++	+++	-	-	+
OEt	OBn	++	+++			++
OPoc	OPoc		+			
OH	OEt		++			
OH	OPh	+++	-			
OH	OBn		+	-	-	

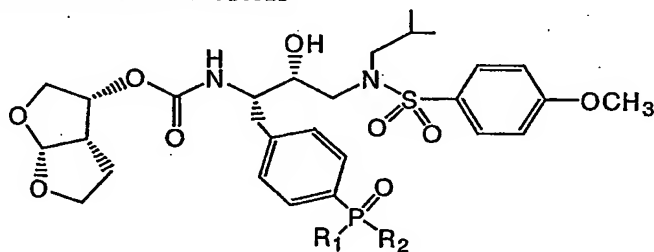
## P1-Phosphonic acid and esters



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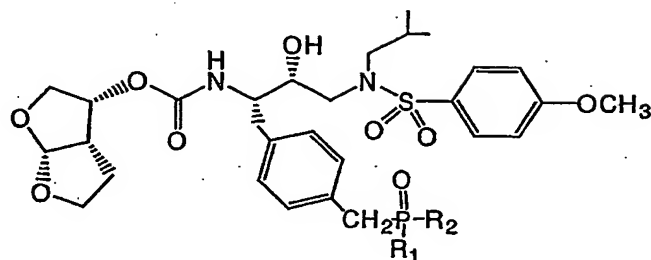
R1	R2	Ki (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> (μM)
OH	OH	+++	+			
Et	Et	+++	+++			

## P1-Direct phosphonic acid and esters



10

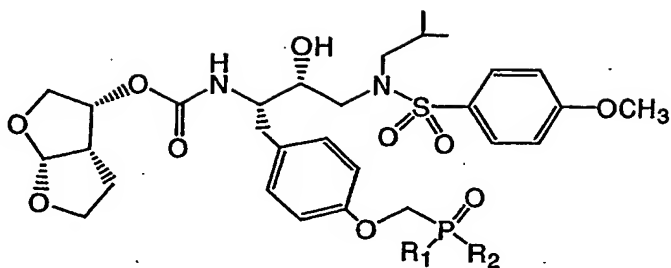
R1	R2	Ki (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
OH	OH	++	-			
OEt	OEt	+++	+++	+	-	

P1-CH<sub>2</sub>-phosphonic acid and esters

5

R1	R2	Ki (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
OE	OE	+++	+++	+	+	

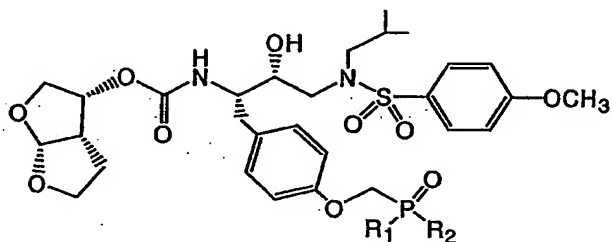
## P1-P-Bisamidates



R1	R2	Ki (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
NHEt	NHEt	+++	++	—	—	
Gly-Et	Gly-Et	++	++			
Gly-Bu	Gly-Bu	+++	+++			
Ala-Et	Ala-Et	++	++		—	—
Ala-Bu	Ala-Bu	++	+++	+	—	
Aba-Et	Aba-Et	+++	+++			
Aba-Bu	Aba-Bu	+++	+++	++	+	
Val-Et	Val-Et	+	+++	—	—	
Leu-Et	Leu-Et	++	+++			
Leu-Bu	Leu-Bu	++	++	+	+	
Phe-Et	Phe-Et		+++			
Phe-Bu	Phe-Bu		+++			

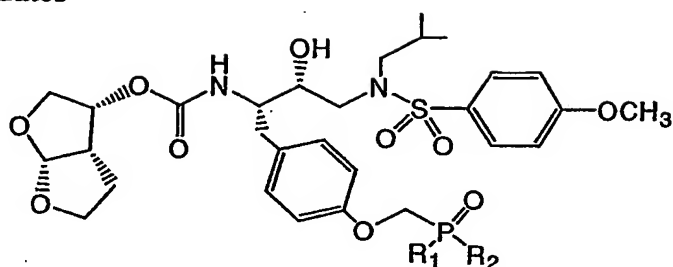
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## P1-P-Bislactates



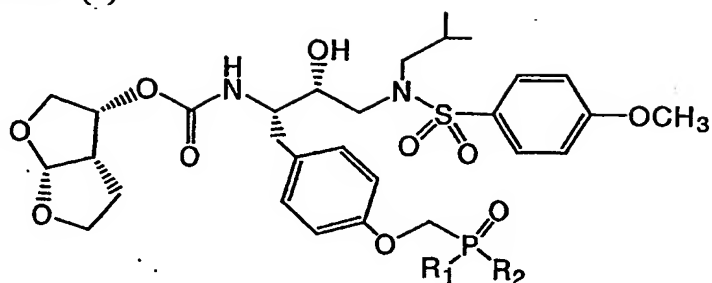
R1	R2	Ki (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
Glc-Et	Glc-Et	+++	+	—	—	
Lac-Et	Lac-Et	++	++	—	—	
Lac-iPr	Lac-iPr	++	+++		—	

## P1-P-Monoamidates



R1	R2	Ki (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
OPh	Gly-Bu	++	++	-	-	
OPh	Ala-Me	++	+++		-	
OPh	Ala-Et	+++	+++	-	-	
OPh	Ala-iPr	++	+++	-	-	
OPh	Ala-iPr	+++	+++			
OPh	Ala-iPr	++	+++			
OPh	(D)Ala-iPr	++	+++		-	
OPh	(D)Ala-iPr	+++	+++			
OPh	(D)Ala-iPr	+++	+++			
OPh	Ala-Bu	++	+++	-	-	
OPh	Ala-Bu	++	+++	-		
OPh	Ala-Bu	++	+++	-		
OPh	Aba-Et		+++			
OPh	Aba-Et		+++	-	-	
OPh	Aba-Et		++			
OPh	Aba-Bu		+++	+	-	
OPh	Aba-Bu		++	-	-	
OBn	Ala-Et	+++	+++	-	-	
OH	Ala-OH	+++	-			
OH	Ala-Bu		-			

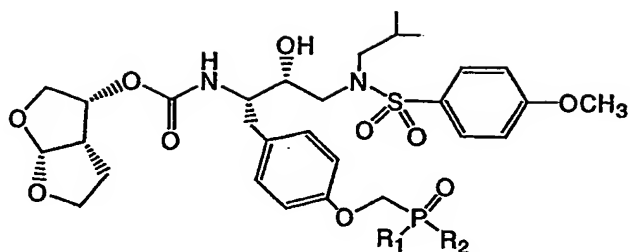
## P1-P-Monolactates (1)



R1	R2	Ki (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I50V (#2) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
OPh	Glc-Et	+++	+++	-		-	
OPh	Lac-Me		++	-			
OPh	Lac-Et		+++	-	+	-	+
OPh	Lac-Et	+++	+++	-		-	
OPh	Lac-Et	++	+++	-		-	
OPh	Lac-iPr	++	+++	-		-	
OPh	Lac-iPr	+++	+++				
OPh	Lac-iPr	++	+++				
OPh	Lac-Bu	++	++			-	
OPh	Lac-Bu	++	++				
OPh	Lac-Bu	++	++				
OPh	Lac-EtMor		-				
OPh	Lac-PrMor		-				
OPh	(R)Lac-Me	+++	+++				
OPh	(R)Lac-Et	+++	+++	-		-	
OEt	Lac-Et		++				
OCH <sub>2</sub> CF <sub>3</sub>	Lac-Et		++				
OBn	Lac-Bn	++	++				
OBn	(R)Lac-Bn						
OH	Lac-OH	+++	+			-	
OH	(R)Lac-OH	++	+			-	



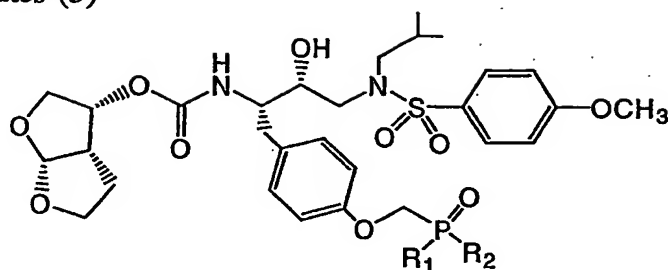
## P1-P-Monolactates (2)



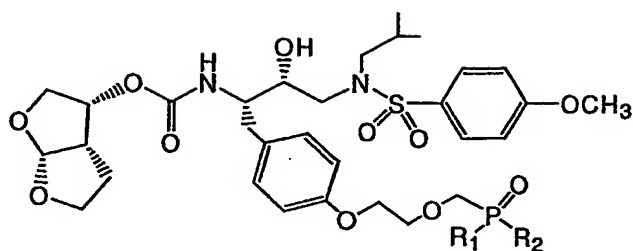
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R1	R2	Ki (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
OPh	mix-Hba-Et	++	+++	+	-	
OPh	(S)Hba-Et	+	+++			
OPh	(S)Hba-tBu		+++			
OH	(S)Hba-OH	++				
OPh	(R)Hba-Et		+++			
OPh	(S)MeBut-Et		+++			
OPh	(R)MeBut-Et		+++			
OPh	DiMePro-Me	++				
OPh	(S)Lac-EtMor		-			
OPh	(S)Lac-PrMor		-			
OPh	(S)Lac-EtPip		++	-	-	

## P1-P-Monolactates (3)

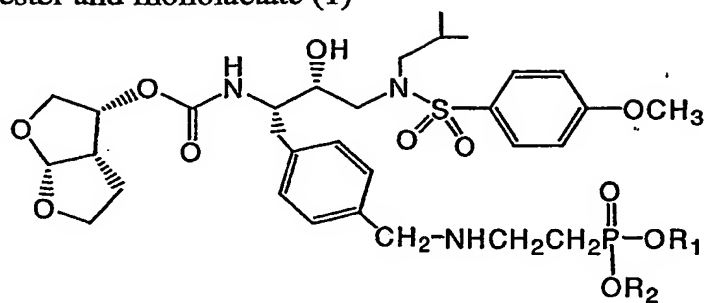


R1	R2	Ki (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
OPh— <i>o</i> -i-But	(S)Lac-Et		+++			
OPh— <i>p</i> -n-Oct	(S)Lac-Et		++			
OPh— <i>p</i> -n-But	(S)Lac-Et		+++			
OPh— <i>m</i> -COOBn	(S)Lac-Et		++			
OPh— <i>m</i> -COOH	(S)Lac-Et		++			
OPh— <i>m</i> -CH <sub>2</sub> OH	(S)Lac-Et		++	—	—	
OPh— <i>m</i> -CH <sub>2</sub> NH <sub>2</sub>	(S)Lac-Et	++	++			
OPh— <i>m</i> -CH <sub>2</sub> NMe <sub>2</sub>	(S)Lac-Et		+			
OPh— <i>m</i> -CH <sub>2</sub> Mor	(S)Lac-Et		++	—	—	
OPh— <i>m</i> -CH <sub>2</sub> Pip	(S)Lac-Et		++			
OPh— <i>m</i> -CH <sub>2</sub> NMeC <sub>2</sub> OM	(S)Lac-Et		++			
OPh— <i>o</i> -OEt	(S)Lac-Et		+++			
ONMe <sub>2</sub>	(S)Lac-Et		++			
OPip	(S)Lac-Et		+			
OMor	(S)Lac-Et		—			

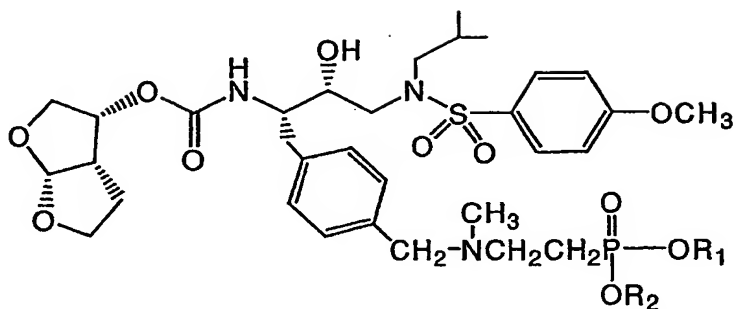
P1-C<sub>2</sub>H<sub>4</sub>-P-Monolactates

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R1	R2	Ki (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
-OC <sub>2</sub> H <sub>4</sub> OBn			+++			
OEt	OEt		+++	-	-	
OPh	Lac-Et		++	-	-	
OH	OH	++				
OH	Lac	++				

P1-CH<sub>2</sub>N-P-diester and monolactate (1)

R <sub>1</sub>	R <sub>2</sub>	Ki (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I50V (#2) fold change	I84V/L9M fold change	CC <sub>50</sub> μM
Et	Et	++	+++		-		
H	H	++	-		+		
Ph	Lac-Et		++	-	++	-	
Ph	Lac-Et		+		+	-	-
Ph	Lac-Et		+		++	-	
Ph	Aba-Et		+		+	-	
Ph-oEt	Lac-Et	++	++	-	++	-	
Ph-dM	Lac-Et		+++		+	+	
Ph-dM	Lac-Pr		+++				
H	Lac	++					
Ph	Hba-Et		++		++	-	
Ph	Hba-Et		++		++	-	+
Ph	Hba-Et		++		++	-	
H	Hba	+					

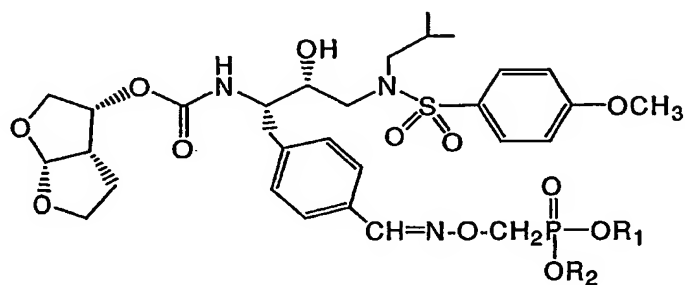
P1-CH<sub>2</sub>N-P-diester and monolactate (2)

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R <sub>1</sub>	R <sub>2</sub>	K <sub>i</sub> (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
Ph	Lac-Et	+	++	+	+	
H	H	++				

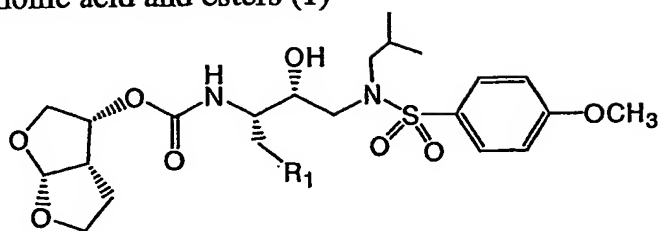
P1-CH<sub>2</sub>N-P-diester and monolactate (3)

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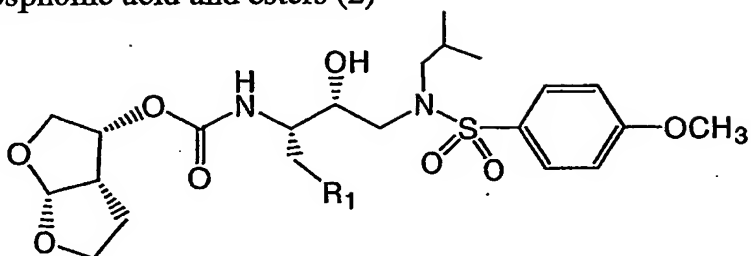
R <sub>1</sub>	R <sub>2</sub>	K <sub>i</sub> (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
Et	Et	++	+++		-	

## P1-N-P1-Phosphonic acid and esters (1)



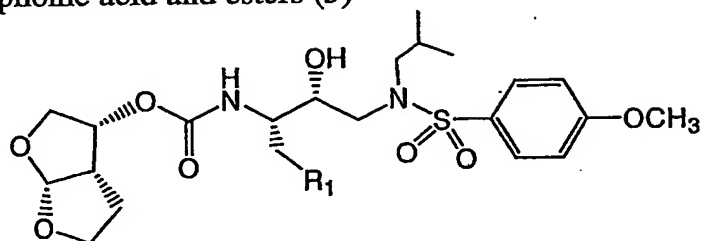
R1	Ki (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
	-	++			
	-	++			
	-				
	++	+++		+	
		-			
	-				
	+	++			
	++	+++		+	
		-			
		-			
	-				
	+	+++		+	

## P1-N-P1-Phosphonic acid and esters (2)



R1	Ki (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
	+	+		+	
	++	+++		+	
	++	+++			
	++	++		-	
		+++			
	++	+++		+	
		+++		-	
	-	+++		++	
	-				
	+	+++	+++	-	
	-				
		+++	++	+	
	-				

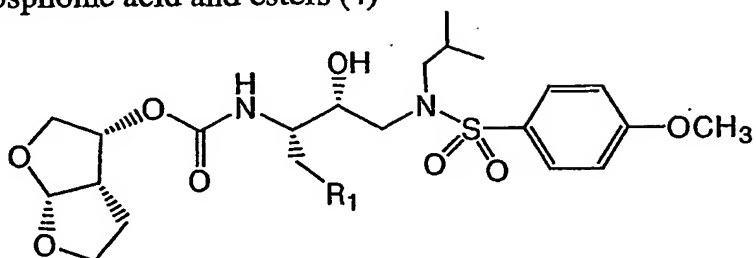
## P1-N-P1-Phosphonic acid and esters (3)



R1	Ki (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
	++	+++	+	+	
	+	++	+	+	
	+	++	+	+	
	+				
	-	-			



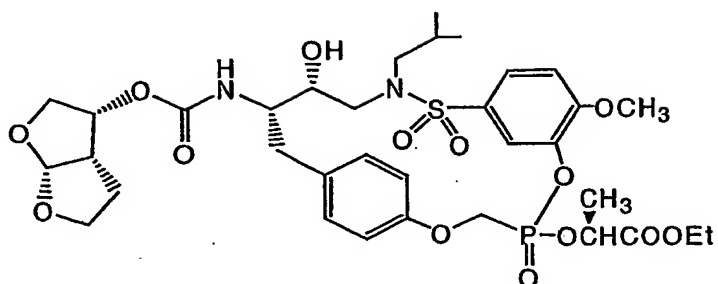
## P1-N-P1-Phosphonic acid and esters (4)



R1	K <sub>i</sub> (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
	+++				
	+++	+++	-	-	
	++	+++	+	-	
	++	+++			
	++	++			
	+++	+++			
		+++	++	-	
		+++	++	-	
	++				
	++				

## P1- P-cyclic monolactate

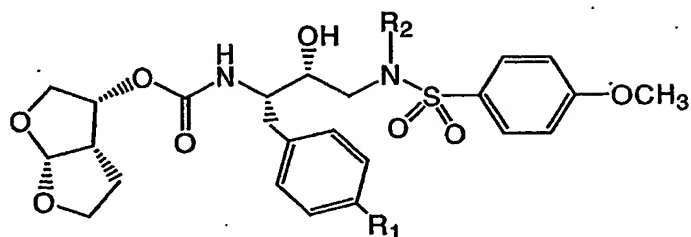
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R <sub>1</sub>	R <sub>2</sub>	K <sub>i</sub> (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
		nd	nd			
		nd	nd			

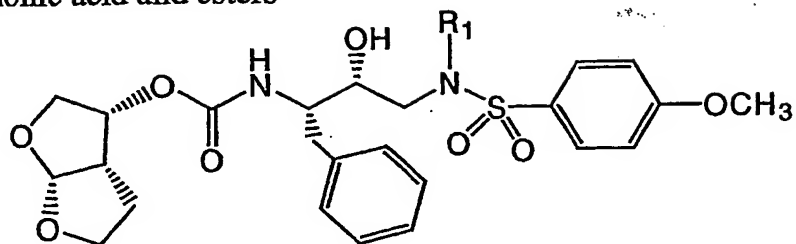
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## P1'-N-P1-Phosphonic acid and esters



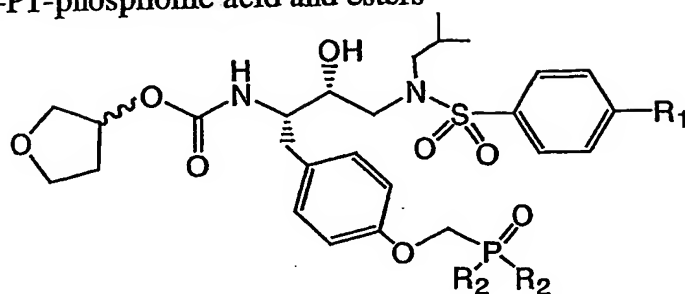
R1	R2	Ki (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
CH <sub>3</sub>		++	+++	++	+	
OH			+++	-	-	
CH <sub>2</sub> OH		+++	+++	-	-	
OBn		+++	+++	-	-	
OH		-	++	-	-	
OBn		-	+++		-	
		-	-	+	+	
		+	++	+	+	
OH		-	-			
		++	-			
		++	-			
		++	++			
		+	-			

## P1'-Phosphonic acid and esters



R1	Ki (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
	++	+++	+++	+++	
	+++	+++	+++	+++	
	++	+		+++	
	+++	+++		+++	
	+++	+++		++	
	++	++	++	++	
	++	+++	+++	+++	

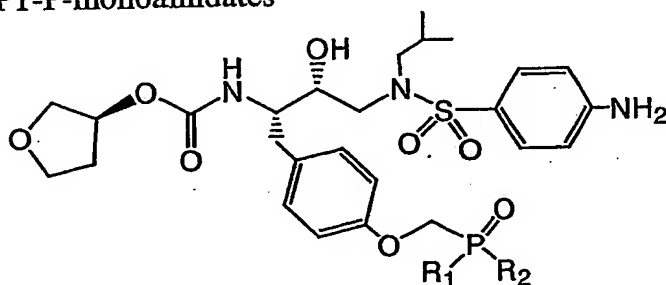
## P2-Monofuran-P1-phosphonic acid and esters



R1	R2	Ki (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
OMe	OH		—	+++	+++	
OMe	OEt	+++	+++	+++	++	
OMe	OBn		+++	++	++	
OMe	phenol	+++	+++	+++	+	
OMe	OEt	++	+++	+++	++	
NH <sub>2</sub>	phenol	+	++	+	—	
NH <sub>2</sub>	OH		—		+	
NH <sub>2</sub>	OBn	++	++		+	

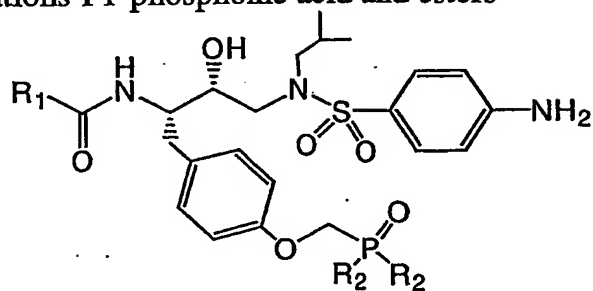
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## P2-Monofuran-P1-P-monoamidates



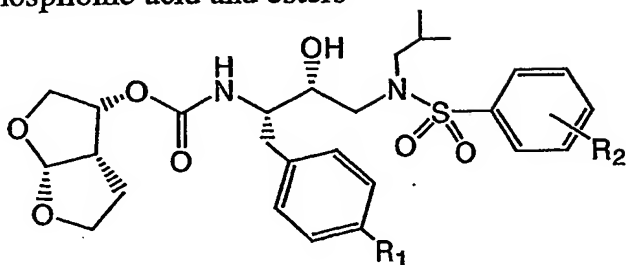
R1	R2	Ki (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
OPh	Ala-iPr	++	++		+	
OPh	Ala-iPr	++	++			
OPh	Ala-iPr	+	++			

## P2-Other modifications-P1-phosphonic acid and esters



R1	R2	Ki (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
	phenyl	+	+++	+++	++	
	phenol	+	++	++	+	
	OH	-	-	++	-	
	OBn	+	++	+	-	
	phenyl	+	++	+++	+	
	OH	+	-	++	+	
	OBn	+	++	+++	+	
	phenyl	-	++		++	
	phenol	+	+		-	
	OH	+	-	-	-	
	OBn	++	++	+	-	

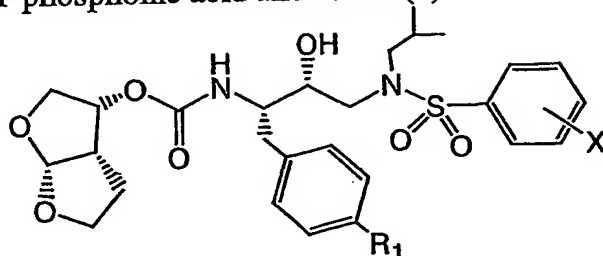
## P2'-Amino-P1-phosphonic acid and esters



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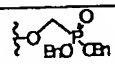
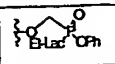
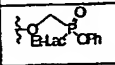
R1	R2	Ki (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
OH	<i>p</i> -NH <sub>2</sub>	++	++	-	-	
	<i>p</i> -NH <sub>2</sub>	++	-	+	-	
	<i>p</i> -NH <sub>2</sub>	++	+++		-	
	<i>p</i> -NO <sub>2</sub>	++	+++		-	
	<i>p</i> -NHEt	++	+++		-	
	<i>p</i> -NH <sub>2</sub>	++	+++	-	-	
OH	<i>m</i> -NH <sub>2</sub>	++	++		-	
	<i>m</i> -NH <sub>2</sub>	++	+		-	
	<i>m</i> -NH <sub>2</sub>	++	++		-	
	<i>m</i> -NH <sub>2</sub>	++	+++	-	-	
	<i>m</i> -NH <sub>2</sub>	+	++	-	-	
	<i>m</i> -NH <sub>2</sub>	++	++			
	<i>m</i> -NH <sub>2</sub>	+	++			

## P2'-Substituted-P1-phosphonic acid and esters (1)

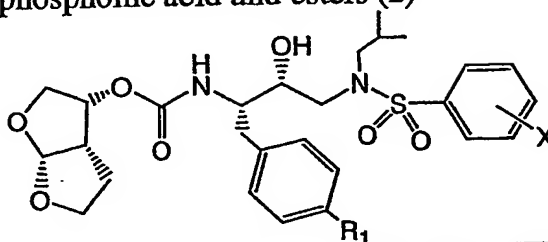


R1	X	Ki (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
	<i>p</i> -OH	+++	+			
	<i>p</i> -OH	+++	+++			
	<i>p</i> -OH	++				
	<i>p</i> -OH		+++		-	
	<i>p</i> -OBn		++			
	<i>p</i> -OBn		-			
	<i>p</i> -H	++	-			
	<i>p</i> -H	++	+++		+	
	<i>p</i> -H		+++	+	+	
	<i>p</i> -H		++			
	<i>p</i> -H	++				
	<i>p</i> -F	++	+			
	<i>p</i> -F	++	+++		+	
	<i>p</i> -F		+++	+	+	
	<i>p</i> -F		++	+	+	
	<i>p</i> -F	++				
	<i>p</i> -CF <sub>3</sub>	+++	+			
	<i>p</i> -CF <sub>3</sub>	++	+++		-	
	<i>p</i> -OCF <sub>3</sub>	++	+			
	<i>p</i> -OCF <sub>3</sub>	++	+++		+	



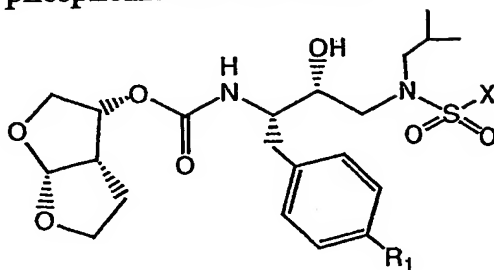
	<i>p</i> -CN	++	+++		-	
	<i>p</i> -Pip	-	-			
	<i>p</i> -Pip-Me	-	-			

## P2'-Substituted-P1-phosphonic acid and esters (2)



R1	X	Ki (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
	<i>m</i> -Py	++	+++			
	<i>m</i> -Py	++				
	<i>m</i> -Py	++	++	+	-	
	<i>m</i> -Py	++	++			
	<i>m</i> -Py	++				
	<i>m</i> -Py-Me <sup>+</sup>		+			
	<i>m</i> -Py-Me <sup>+</sup>		++			
	<i>m</i> -Py-oxide		++			
	<i>m</i> -Py-oxide	++				
	<i>m</i> -Py-oxide	++	++		-	
	<i>m</i> -Py-oxide	+				
	<i>m</i> -Py-oxide		-			
<i>p</i> -Py-oxide	<i>p</i> -OMe	++	-			
	<i>p</i> -CHO		+++			
	<i>p</i> -CHO		+++			
	<i>p</i> -CH <sub>2</sub> OH		+++	-	-	
	<i>p</i> -CH <sub>2</sub> OH	++				
	<i>p</i> -CH <sub>2</sub> OH	++				
	<i>p</i> -CH <sub>2</sub> Mor		++	-	-	
	<i>p</i> -CH <sub>2</sub> Mor	-				
	<i>p</i> -CH <sub>2</sub> Mor	-				

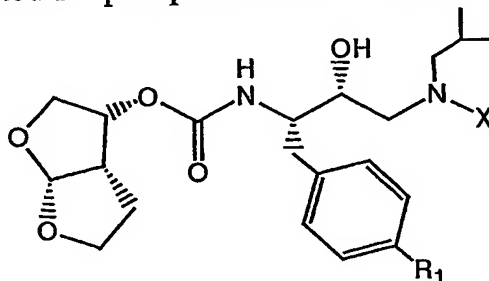
## P2'-Alkylsulfonyl-P1-phosphonic acid and esters



R1	X	Ki (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
		-	-			
		+	++			

5

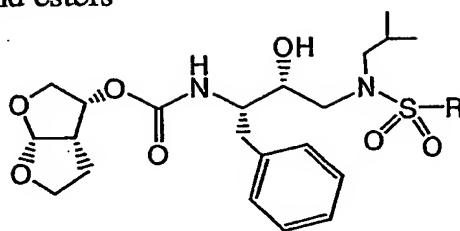
## P2'-Carbonyl-substituted-P1-phosphonic acid and esters



R1	X	Ki (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
		-				
		-	++			
			+			

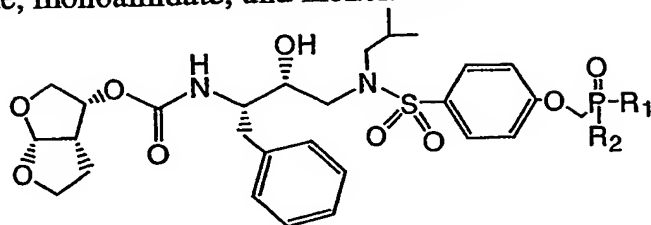
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## P2'-Phosphonic acid and esters



R	K <sub>i</sub> (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
	+++	+++	-	-	
	+++	+	-	-	
	++	-			
	++	+++	++	++	
	+	++	+++	+++	
	+++	+++	+	+	
	+++	+++	+++	++	
	++	++	++	+	
	+++	+++	+++	++	
	++	+++	++	++	
	+++	+++	-	-	
	+++	++	+	-	
	+	++	+	+	
	-	+	+++	++	
	+	++	+	-	

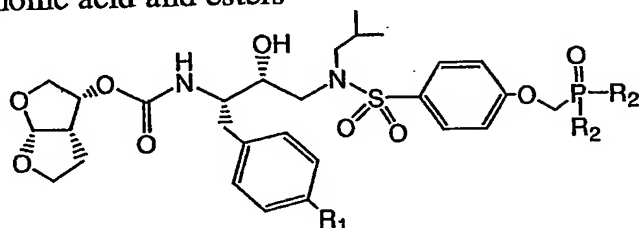
## P2'-P-Bisamidate, monoamidate, and monolactate



R <sub>1</sub>	R <sub>2</sub>	K <sub>i</sub> (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
Ala-Bu	Ala-Bu	+	++	+	+	
OPh	Ala-iPr	++	++			
OPh	Lac-iPr	+	+			
OH	Ala-OH	++				

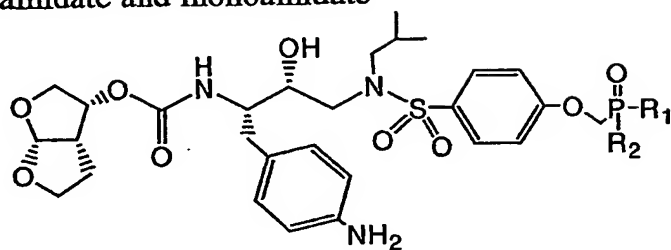
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## P1-N-P2'-Phosphonic acid and esters



R <sub>1</sub>	R <sub>2</sub>	K <sub>i</sub> (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
NO <sub>2</sub>	phenol		+++	-		
NH <sub>2</sub>	OH	++	-			
NH <sub>2</sub>	OE <sub>t</sub>	+	++		++	
NH <sub>2</sub>	OBn	+	+		+	
NMe <sub>2</sub>	OE <sub>t</sub>	++	+++		++	
OH	OH	++	-			
OH	OBn	++	++			
OC <sub>2</sub> H <sub>4</sub> NMe <sub>2</sub>	OH	+++	+			
OC <sub>2</sub> H <sub>4</sub> -NMe <sub>2</sub>	OBn	++	++			

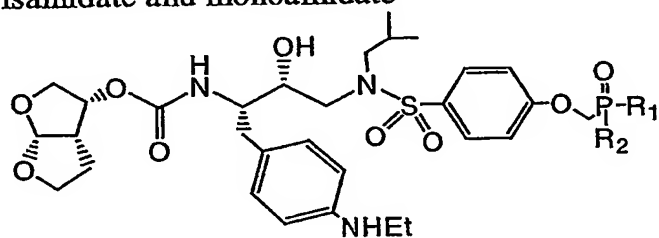
## P1-N-P2'-P-Bisamidate and monoamidate



R <sub>1</sub>	R <sub>2</sub>	K <sub>i</sub> (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
Ala-Bu	Ala-Bu	+	+			
OPh	Ala-iPr	+	-			
OPh	Ala-iPr	++	-			

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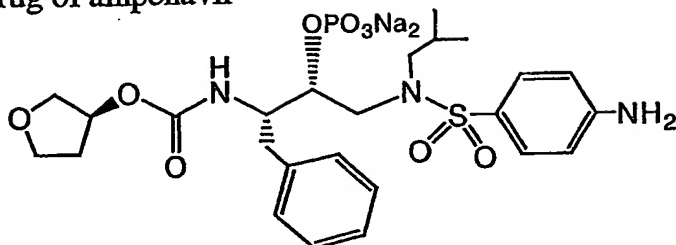
## P1-NEt-P2'-P-Bisamidate and monoamidate



R <sub>1</sub>	R <sub>2</sub>	K <sub>i</sub> (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
OPh	Ala-iPr	+	+			
OPh	Ala-iPr	+	+	-	-	

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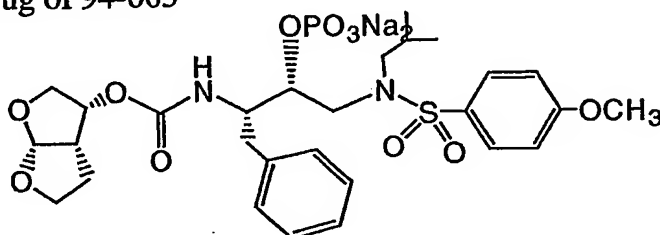
## Phosphate prodrug of ampenavir



R <sub>1</sub>	R <sub>2</sub>	K <sub>i</sub> (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
			++			

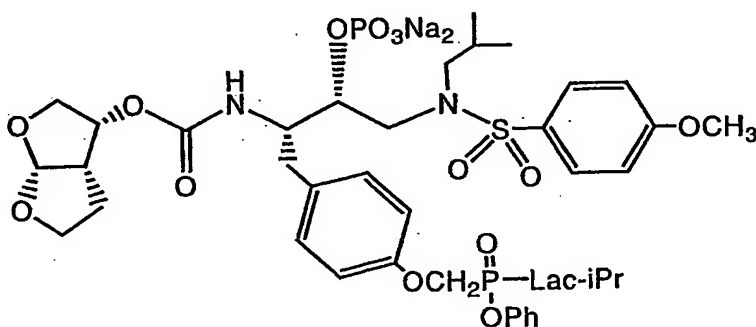
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## Phosphate prodrug of 94-003



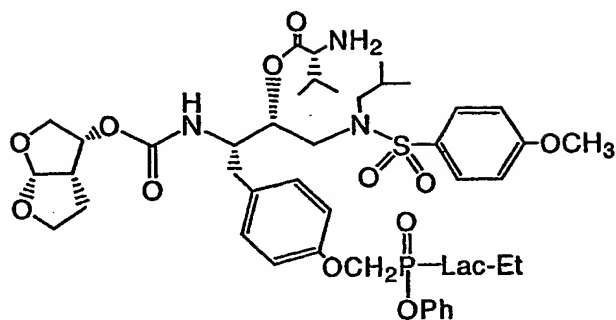
R <sub>1</sub>	R <sub>2</sub>	K <sub>i</sub> (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
			+++			

## 10 Phosphate prodrug of GS77366 (P1-mono(S)Lac-iPr)



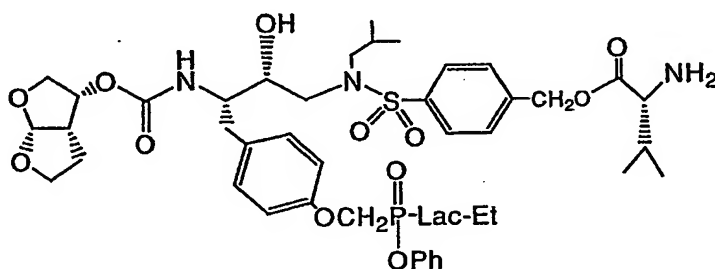
R <sub>1</sub>	R <sub>2</sub>	K <sub>i</sub> (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
			+++			

## Valine prodrug of (P1-mono(S)Lac-Et)



R <sub>1</sub>	R <sub>2</sub>	K <sub>i</sub> (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
			++			

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Valine prodrug of GS278053 (P1-mono(S)Lac-Et,P2'-CH<sub>2</sub>OH)

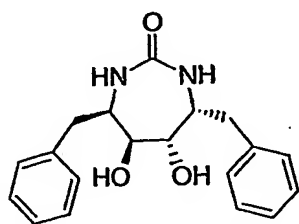
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R <sub>1</sub>	R <sub>2</sub>	K <sub>i</sub> (pM)	EC <sub>50</sub> (nM)	I50V (#1) fold change	I84V/L90M fold change	CC <sub>50</sub> μM
			++			

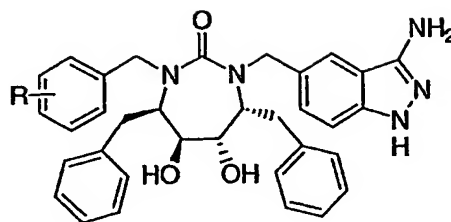


Table 11: Enzymatic and Cellular Activity Data

## Formula VIIa CCLPPI activity



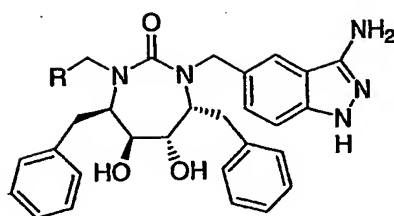
DMP-850



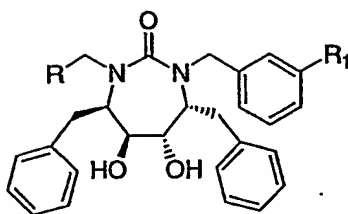
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Structure, R	Enzymatic assay			Cell-based assay (MT-4) EC <sub>50</sub> / nM						
	K <sub>i</sub> (nM)	WT IC <sub>50</sub> / nM	84V9 OM IC <sub>50</sub> / nM	WT	84V9 OM	30N 82I88 D	48V54 V82A	48V54 V82S	48V82 A90M	46I50V
H (DMP-850)	0.033	3.0	9.1	165	819	82	82	73	45	88
p-OH	0.029	3.0	12	149	143	79	32	39	19	55
p-OBn	>5	353	781	2123	5312	1548	ND	ND	ND	ND
p-OCH <sub>2</sub> PO <sub>3</sub> Bn <sub>2</sub>	>5	276	2042	2697	4963	2119	ND	ND	ND	ND
p-OCH <sub>2</sub> PO <sub>3</sub> Et <sub>2</sub>	>5	627	1474	2480	>6000	1340	ND	ND	ND	ND
p-OCH <sub>2</sub> PO <sub>3</sub> H <sub>2</sub>	>5	551	1657	>12000	ND	ND	ND	ND	ND	ND
m-OH	0.128	1.6	12	151	475	249	84			104
m-OBn	0.253	6.9	27	218	2422	82	709	ND	ND	601
m-OCH <sub>2</sub> PO <sub>3</sub> Bn <sub>2</sub> (N-iPr indazole)	1.54 <sup>a</sup>	31	72	489	514	237	159	171	168	708
m-OCH <sub>2</sub> PO <sub>3</sub> Bn <sub>2</sub>	0.177	18	43	898	>6000	705	2597	ND	ND	3121
m-OCH <sub>2</sub> PO <sub>3</sub> Et <sub>2</sub>	1.93 <sup>a</sup>	70	169	665	3005	93	513	ND	ND	857
m-OCH <sub>2</sub> PO <sub>3</sub> H <sub>2</sub>	0.254	8.3	33	>12000	ND	ND	ND	ND	ND	ND

m-OCH <sub>2</sub> PO <sub>3</sub> Ph <sub>2</sub>	0.543 <sub>a</sub>	10	42	1349	>600 0	1541	2183	ND	ND	3380
m-OCH <sub>2</sub> PO <sub>3</sub> HPh	0.644	17	65	1745	>600 0	ND	ND	ND	ND	ND
m-mono-Ala-Bu	0.858 <sub>a</sub>	6.6	39	1042	>600 0	425	790	ND	ND	797
m-mono-Ala-Et <sup>†</sup>		35	68	1436	>600 0	219	734	ND	ND	1350
m-mono-Lac-Bu		15	34	2663	>600 0	1089	ND	ND	ND	ND
m-mono-Lac-Et		23	80	2609	>600 0	516	5923	ND	ND	>6000
m-bis-Ala-Bu	1.279 <sub>a</sub>	18	103	1079	>600 0	2362	1854	ND	ND	1536
m-bis-Ala-Et	1.987 <sub>a</sub>	31	202	5620	>600 0	1852	ND	ND	ND	ND

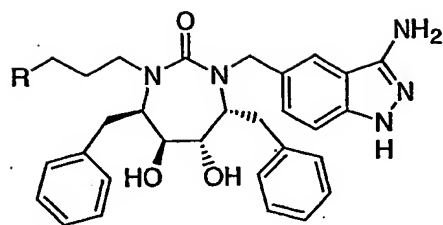


Structure, R	Enzymatic assay			Cell-based assay (MT-4) EC <sub>50</sub> / nM						
	K <sub>i</sub> (nM)	WT IC <sub>50</sub> nM	84V9 0M IC <sub>50</sub> / nM	WT	84V90 M	30N 82I88 D	48V5 4V82 A	48V54 V82S	48V82A 90M	46I50 V
H (DMP-850)	0.033	3.0	9.1	165	819	82	82	73	45	88
	0.091	3.4	27	1548	>6000	>6000	ND	ND	ND	ND
	0.354	3.3	25	168	909	750	277			489
	0.157	1.6	10	188	476	666	240			319
	0.044	5.0	27	491	387	234	238			192
	0.362	7.3	70	5141	>6000	4480	ND	ND	ND	ND
	0.112	1.4	6.4	603	1276	678	208			209
	<0.03	1.3	7.5	625	708	899	301			398



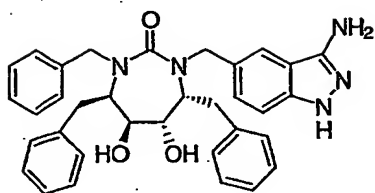
Structure, R1	Structure, R	Enzymatic assay			Cell-based assay (MT-4) EC <sub>50</sub> / nM						
		K <sub>i</sub> (nM)	WT IC <sub>50</sub> / nM	84 V9 0M IC <sub>50</sub> / nM	WT	84V90 M	30N 82I8 8D	48V 54V 82A	48V5 4V82 S	48V8 2A90 M	46L50V
CO <sub>2</sub> H			15	174	3055	>6000	887	ND	ND	ND	ND
CONH(CH <sub>2</sub> ) <sub>3</sub> PO <sub>3</sub> Et <sub>2</sub>		0.009	1.1	12	65	311	74	80	75	74	85
CO <sub>2</sub> H			18	299	2344	>6000	3360	ND	ND	ND	ND
CONH(CH <sub>2</sub> ) <sub>3</sub> PO <sub>3</sub> Et <sub>2</sub>		<0.004	2.3	29	176	824	171	233	ND	ND	195
CO <sub>2</sub> H		0.091	3.4	27	1548	>6000	>6000	ND	ND	ND	ND
CONH(CH <sub>2</sub> ) <sub>3</sub> PO <sub>3</sub> Et <sub>2</sub>		0.157	1.6	10	188	476	666	240			319

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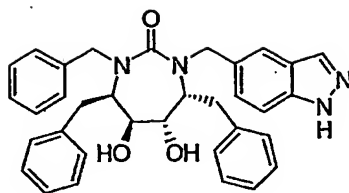


Structure, R	Enzymatic assay			Cell-based assay (MT-4) EC <sub>50</sub> / nM						
	K <sub>i</sub> (nM)	WT IC <sub>50</sub> / nM	84V90 M IC <sub>50</sub> / nM	WT	84V90 M	30N 82I88D	48V5 4V82 A	48V5 4V82 S	48V82 A90M	46I50 V
CH <sub>3</sub> (DMP-851)	0.033	3.8	9.4	54	918	69	33	30	22	17
OH	0.65 <sup>a</sup>	6.1	77	356	2791	669	294	ND	ND	683
OCH <sub>2</sub> PO <sub>3</sub> Et <sub>2</sub>	1.230 <sup>a</sup>	23	157	356	>6000	145	175	ND	ND	138
OCH <sub>2</sub> PO <sub>3</sub> H <sub>2</sub>	0.809	59	137	1074	>6000	ND	ND	ND	ND	ND
O-mono-Lac-Et	>2.0	93	553	>6000	>6000	ND	ND	ND	ND	ND
O-mono-Lac-Bu	>2.0	25	249	>6000	>6000	ND	ND	ND	ND	ND
CH <sub>2</sub> OH	0.017	2.8	31	253	1106	486	413	ND	ND	524
CH <sub>2</sub> OCH <sub>2</sub> PO <sub>3</sub> Et <sub>2</sub>	2.8	13	123	119	3295	267	430	ND	ND	789
CH <sub>2</sub> OCH <sub>2</sub> PO <sub>3</sub> H <sub>2</sub>		42	205	1757	>4243	ND	ND	ND	ND	ND

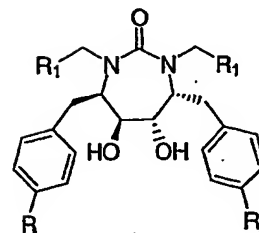
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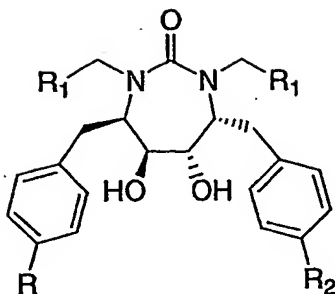


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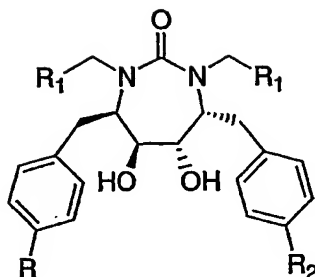
R	R1	R2	Enzymatic assay			Cell-based assay (MT-4) EC <sub>50</sub> / nM						
			K <sub>i</sub> (nM)	WT IC <sub>50</sub> / nM	84V9 OM IC <sub>50</sub> / nM	WT	84V9 OM	30N 82I88 D	48V5 4V82 A	48V5 4V82 S	48V8 2A90 M	46I50 V
—	—	—	0.033	3.0	9.1	165	819	82	82	73	45	88
—	—	—	0.374	5.8	43.3	193	2312	281	705	ND	ND	772
H	Ph	H		34	631	2492	>600	3360	ND	ND	ND	ND
OH	Ph	OH		31	397	117	5609	756	2266	ND	ND	928
OH	Ph	OCH <sub>2</sub> PO <sub>3</sub>		9	40	33	791	92	807	1103	1429	53
H	Ph	OCH <sub>2</sub> PO <sub>3</sub>	0.656	3.9	48	107	2456	293	1438	1899	3292	589
H	Indazol	H	<0.01	2.5	13	11	22	<8	5.5	8	4	4.0
OH	Indazol	OH	0.012	0.6	3.5	>600	2728	7224	ND	ND	ND	ND
OH	Indazol	OCH <sub>2</sub> PO <sub>3</sub>	0.137	1.1	5.5	1698	1753	1998	ND	ND	ND	ND
H	Indazol	OCH <sub>2</sub> PO <sub>3</sub>	0.028	1.4	6.2	57	40	68	28	26	32	27

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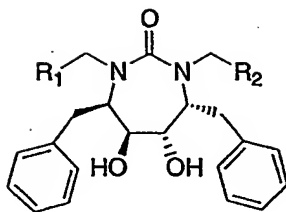
			Enzymatic		Cell-based assay (MT-4) EC <sub>50</sub> / nM							
R	R1	R2	K <sub>i</sub> (nM)	WT IC <sub>50</sub> / nM	84V9 OM IC <sub>50</sub> / nM	WT	84V9 OM	30N 82I8 8D	48V5 4V82 A	48V5 4V82 S	48V 82A 90M	46L50 V
—	—	—	0.033	3.0	9.1	165	819	82	82	73	45	88
OH	Ph	OCH <sub>2</sub> PO <sub>3</sub> Et <sub>2</sub>		9	40	33	791	92	807	1103	1429	53
H	Ph	OCH <sub>2</sub> PO <sub>3</sub> Et <sub>2</sub>	0.656	3.9	48	107	2456	293	1438	1899	3292	589
OCH <sub>3</sub>	Ph	OCH <sub>2</sub> PO <sub>3</sub> Et <sub>2</sub>										
OH	Ph-pOH	OCH <sub>2</sub> PO <sub>3</sub> Et <sub>2</sub>	<0.01	2.6	18	285	1912	211	986	ND	ND	1107
H	Ph-pOH	OCH <sub>2</sub> PO <sub>3</sub> Et <sub>2</sub>	0.319	2.1	33	65	272	90	128	198	126	144
OCH <sub>3</sub>	Ph-pOH	OCH <sub>2</sub> PO <sub>3</sub> Et <sub>2</sub>	0.045	1.8	17	29	146	23	67	106	48	68
OH	Ph-mNH <sub>2</sub> /NHEt	OCH <sub>2</sub> PO <sub>3</sub> Et <sub>2</sub>		8.7	67	286	1902	562	789	1781	684	239
H	Ph-mNH <sub>2</sub>	OCH <sub>2</sub> PO <sub>3</sub> Et <sub>2</sub>	0.126	3.4	39	65	328	16	168	146	74	46
OCH <sub>3</sub>	Ph-mNH <sub>2</sub>	OCH <sub>2</sub> PO <sub>3</sub> Et <sub>2</sub>	<0.01	3.6	56	63	535	18	202	117	102	36
OCH <sub>3</sub>	m- pyridine	OCH <sub>2</sub> PO <sub>3</sub> Et <sub>2</sub>				115	765	106	1019	970	480	352



			Enzymatic assay		Cell-based assay (MT-4) EC <sub>50</sub> / nM							
R	R1	R2	K <sub>i</sub> (nM)	WT IC <sub>50</sub> / nM	84 V9 0M IC <sub>50</sub> / nM	WT	84V9 0M	30N 82I88 D	48V54 V82A	48V5 4V82 S	48V8 2A90 M	46I50 V
—	—	—	0.033	3.0	9.1	165	819	82	82	73	45	88
H	Ph-mNH <sub>2</sub>	OCH <sub>2</sub> PO <sub>3</sub> Et <sub>2</sub>	0.126	3.4	39	65	328	16	168	146	74	46
OC H <sub>3</sub>	Ph-mNH <sub>2</sub>	OCH <sub>2</sub> PO <sub>3</sub> Et <sub>2</sub>	<0.01	3.6	56	63	535	18	202	117	102	36
OC H <sub>3</sub>	Ph-mNH <sub>2</sub>	O(CH <sub>2</sub> ) <sub>2</sub> PO <sub>3</sub> Et <sub>2</sub>										
OC H <sub>3</sub>	Ph-mNH <sub>2</sub>	OCONH (CH <sub>2</sub> ) <sub>2</sub> PO <sub>3</sub> Et <sub>2</sub>		11. 3	116	74	2265	77	262	214	215	184
OC H <sub>3</sub>	Ph-mNH <sub>2</sub>	OCONH (CH <sub>2</sub> ) <sub>2</sub> PO <sub>3</sub> Et <sub>2</sub>		9.9	85	58	2151	68	223	203	185	104
H	Ph-pOH	OCH <sub>2</sub> PO <sub>3</sub> Et <sub>2</sub>	0.319	2.1	33	65	272	90	128	222	146	144
OC H <sub>3</sub>	Ph-pOH	OCH <sub>2</sub> PO <sub>3</sub> Et <sub>2</sub>	0.045	1.8	17	30	148	25	70	129	54	90
OC H <sub>3</sub>	Ph-pOH	OCONH (CH <sub>2</sub> ) <sub>2</sub> PO <sub>3</sub> Et <sub>2</sub>		6.6	49	33	495	31	74	51	55	223
—	—	—	0.033	3.0	9.1	165	819	82	82	73	45	88
H	Ph	OCH <sub>2</sub> PO <sub>3</sub> Et <sub>2</sub>	0.656	3.9	48	107	2456	293	1438	1899	3292	589
H	Ph	OH	0.330	15	162	1261	>600 0	2952	>6000			
H	Ph	OCH <sub>2</sub> PO <sub>3</sub> Bn <sub>2</sub>	0.125	7.4	158	1769	>600 0	3135	>6000			
H	Ph	OCH <sub>2</sub> PO <sub>3</sub> H <sub>2</sub>	0.386	9.7	210	>600	>600	ND	ND			



						0	0					
H	Ph	Mono-lac-Et	0.120	6.6	56	1726	>600 0	2793	>6000			
H	Ph	Mono-Ala-Et		5	50	310	2943	238	2851	1948	2450	1250



R1	R2	Enzymatic assay			Cell-based assay (MT-4) EC <sub>50</sub> / nM						
		K <sub>i</sub> (nM)	WT IC <sub>50</sub> / nM	84V 90 M IC <sub>50</sub> / nM	WT	84V 90M	30N 82I88 D	48V 54V 82A	48V54 V82S	48V82 A90M	46I5 0V
Phenyl		0.03	3.0	9.1	165	819	82	82	73	45	88
Phenyl		0.42	6.6	85	1226	>600	869	774	ND	ND	937
Phenyl		0.37	5.8	43.3	193	2312	281	705	ND	ND	772
Phenyl			109	>25	>6000	ND	ND	ND	ND	ND	ND
Phenyl											
Phenyl											
Phenyl											
		1.43	302	114	>6000	>600	ND	ND	ND	ND	ND
		>5	>25	ND	5949	ND	ND	ND	ND	ND	ND
		>5	130	348	2006	3121	ND	ND	ND	ND	ND

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All publications and patent applications cited herein are incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

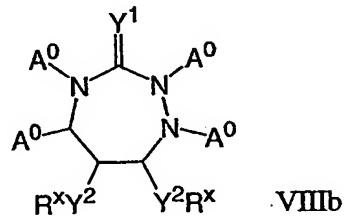
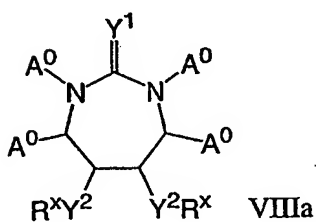
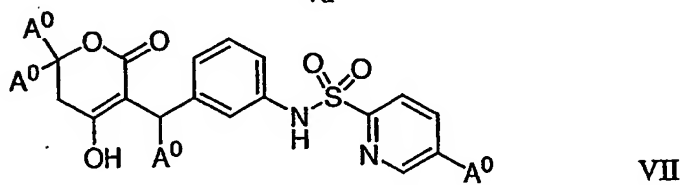
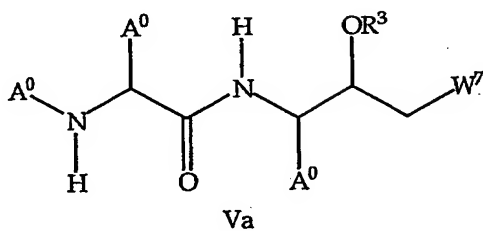
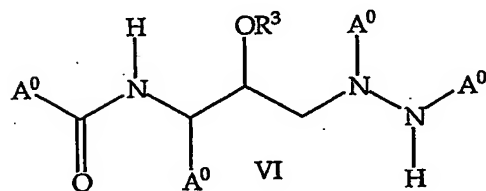
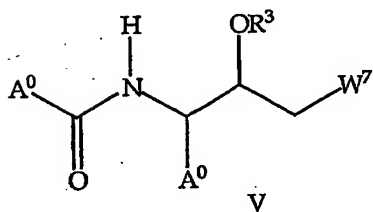
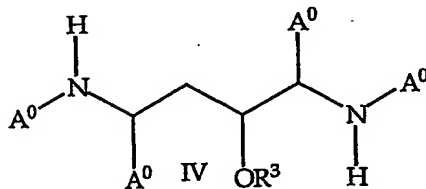
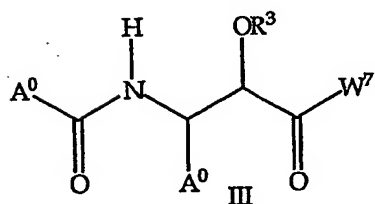
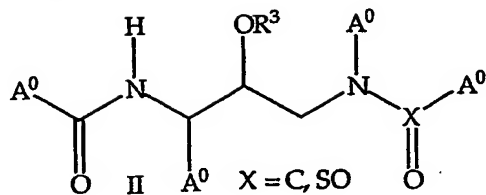
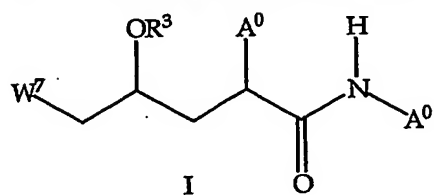
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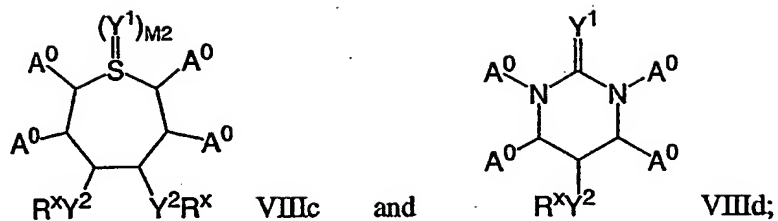
Although certain embodiments have been described in detail above, those having ordinary skill in the art will clearly understand that many modifications are possible in the embodiments without departing from the teachings thereof. All such modifications are intended to be encompassed within the claims of the invention.

In the following claims, the subscript and superscripts of a given variable are distinct.  
For example, R<sub>1</sub> is distinct from R<sup>1</sup>.

1. An HIV protease inhibitor compound comprising a phosphonate group.
2. An HIV protease inhibitor compound of claim 1 selected from:
  - a Saquinavir-like phosphonate protease inhibitor compound,
  - a Lopinavir-like phosphonate protease inhibitor compound,
  - a Ritonavir-like phosphonate protease inhibitor compound,
  - a Indinavir-like phosphonate protease inhibitor compound,
  - a Atazanavir-like phosphonate protease inhibitor compound,
  - a Nelfinavir-like phosphonate protease inhibitor compound,
  - a Tipranavir-like phosphonate protease inhibitor compound,
  - a Amprenavir-like phosphonate protease inhibitor compound,
  - a KNI-like phosphonate protease inhibitor compound, and
  - a Cyclic Carbonyl-like phosphonate protease inhibitor compound;and pharmaceutically acceptable salts, hydrates, and formulations thereof.

3. A compound selected from the Formulas:

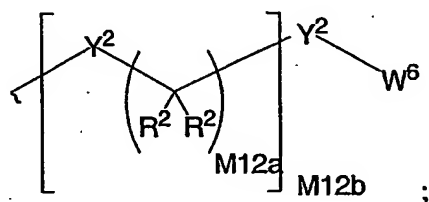




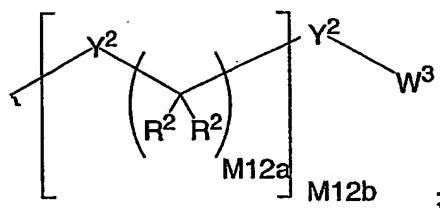
wherein:

$A^0$  is  $A^1$ ,  $A^2$  or  $W^3$  with the proviso that the compound includes at least one  $A^1$ ;

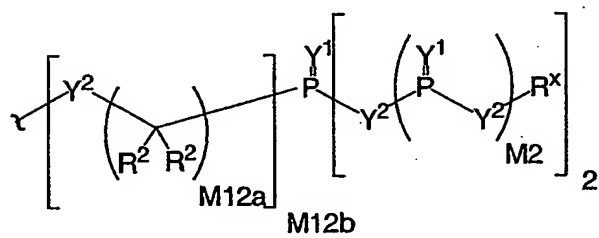
5  $A^1$  is:



$A^2$  is:



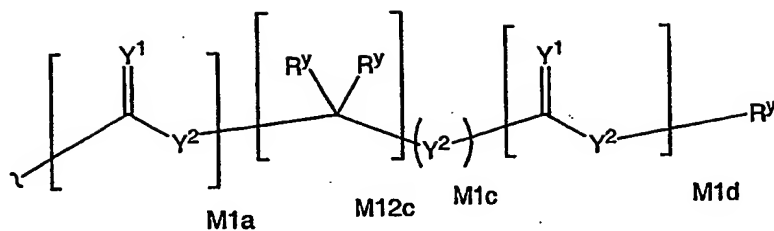
10  $A^3$  is:



$Y^1$  is independently O, S,  $N(R^x)$ ,  $N(O)(R^x)$ ,  $N(OR^x)$ ,  $N(O)(OR^x)$ , or  $N(N(R^x)(R^x))$ ;

$Y^2$  is independently a bond, O,  $N(R^x)$ ,  $N(O)(R^x)$ ,  $N(OR^x)$ ,  $N(O)(OR^x)$ ,  $N(N(R^x)(R^x))$ ,  $-S(O)_{M2}-$ , or  $-S(O)_{M2}-S(O)_{M2}-$ ;

15  $R^x$  is independently H,  $R^1$ ,  $W^3$ , a protecting group, or the formula:



$\text{R}^Y$  is independently H,  $\text{W}^3$ ,  $\text{R}^2$  or a protecting group;

$\text{R}^1$  is independently H or an alkyl of 1 to 18 carbon atoms;

$\text{R}^2$  is independently H,  $\text{R}^1$ ,  $\text{R}^3$  or  $\text{R}^4$  wherein each  $\text{R}^4$  is independently substituted with 0 to 3  $\text{R}^3$  groups, or taken together at a carbon atom, two  $\text{R}^2$  groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3  $\text{R}^3$  groups;

$\text{R}^3$  is  $\text{R}^{3a}$ ,  $\text{R}^{3b}$ ,  $\text{R}^{3c}$  or  $\text{R}^{3d}$ , provided that when  $\text{R}^3$  is bound to a heteroatom, then  $\text{R}^3$  is  $\text{R}^{3c}$  or  $\text{R}^{3d}$ ;

$\text{R}^{3a}$  is F, Cl, Br, I, -CN,  $\text{N}_3$  or  $-\text{NO}_2$ ;

$\text{R}^{3b}$  is  $\text{Y}^1$ ;

$\text{R}^{3c}$  is  $-\text{R}^x$ ,  $-\text{N}(\text{R}^x)(\text{R}^x)$ ,  $-\text{SR}^x$ ,  $-\text{S}(\text{O})\text{R}^x$ ,  $-\text{S}(\text{O})_2\text{R}^x$ ,  $-\text{S}(\text{O})(\text{OR}^x)$ ,  $-\text{S}(\text{O})_2(\text{OR}^x)$ ,  $-\text{OC}(\text{Y}^1)\text{R}^x$ ,  $-\text{OC}(\text{Y}^1)\text{OR}^x$ ,  $-\text{OC}(\text{Y}^1)(\text{N}(\text{R}^x)(\text{R}^x))$ ,  $-\text{SC}(\text{Y}^1)\text{R}^x$ ,  $-\text{SC}(\text{Y}^1)\text{OR}^x$ ,  $-\text{SC}(\text{Y}^1)(\text{N}(\text{R}^x)(\text{R}^x))$ ,  $-\text{N}(\text{R}^x)\text{C}(\text{Y}^1)\text{R}^x$ ,  $-\text{N}(\text{R}^x)\text{C}(\text{Y}^1)\text{OR}^x$ , or  $-\text{N}(\text{R}^x)\text{C}(\text{Y}^1)(\text{N}(\text{R}^x)(\text{R}^x))$ ;

$\text{R}^{3d}$  is  $-\text{C}(\text{Y}^1)\text{R}^x$ ,  $-\text{C}(\text{Y}^1)\text{OR}^x$  or  $-\text{C}(\text{Y}^1)(\text{N}(\text{R}^x)(\text{R}^x))$ ;

$\text{R}^4$  is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

$\text{R}^5$  is  $\text{R}^4$  wherein each  $\text{R}^4$  is substituted with 0 to 3  $\text{R}^3$  groups;

$\text{W}^3$  is  $\text{W}^4$  or  $\text{W}^5$ ;

$\text{W}^4$  is  $\text{R}^5$ ,  $-\text{C}(\text{Y}^1)\text{R}^5$ ,  $-\text{C}(\text{Y}^1)\text{W}^5$ ,  $-\text{SO}_2\text{R}^5$ , or  $-\text{SO}_2\text{W}^5$ ;

$\text{W}^5$  is carbocycle or heterocycle wherein  $\text{W}^5$  is independently substituted with 0 to 3  $\text{R}^2$  groups;

$\text{W}^6$  is  $\text{W}^3$  independently substituted with 1, 2, or 3  $\text{A}^3$  groups;

$\text{W}^7$  is a heterocycle bonded through a nitrogen atom of said heterocycle and independently substituted with 0, 1 or 2  $\text{A}^0$  groups;

M2 is 0, 1 or 2;

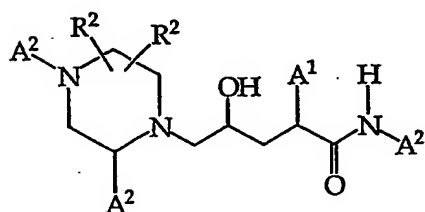
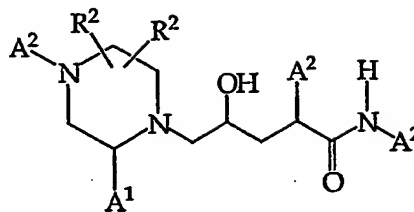
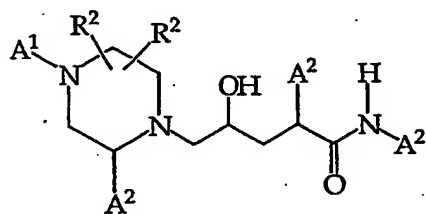
M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

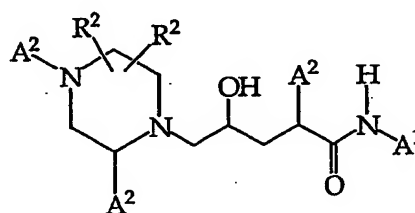
M1a, M1c, and M1d are independently 0 or 1; and

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

4. A compound of claim 3 selected from:

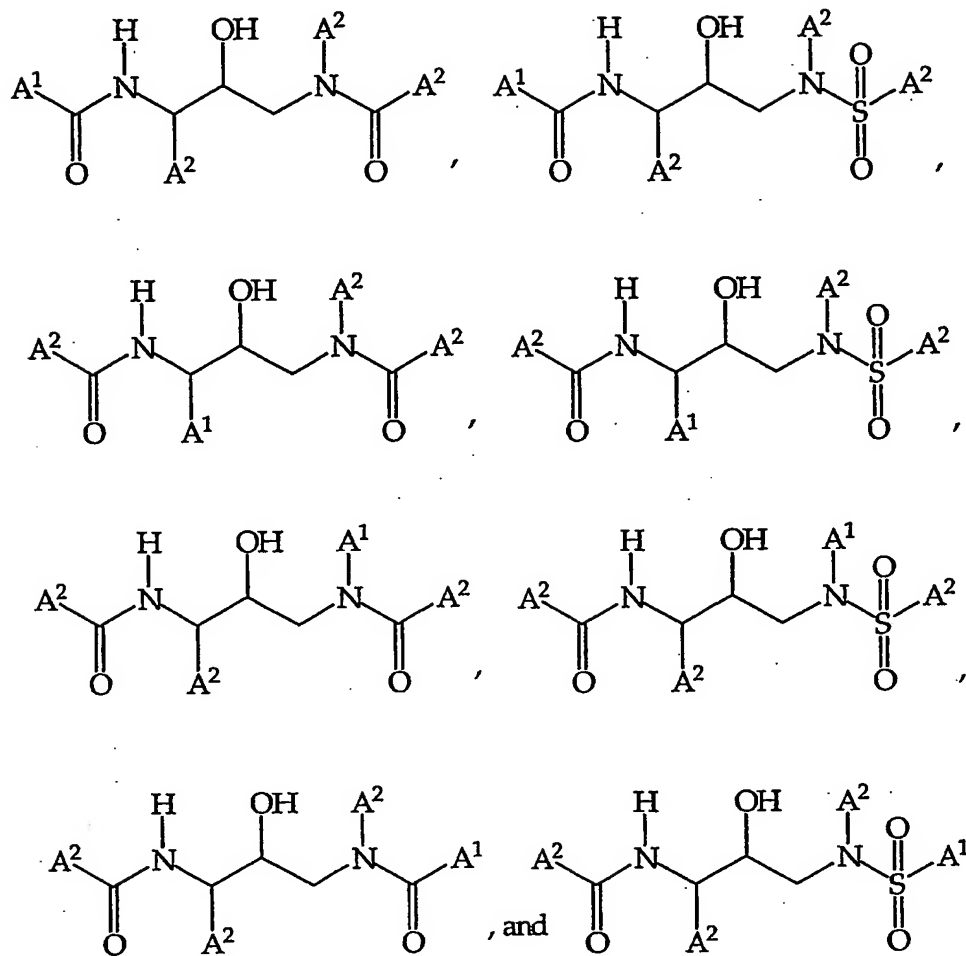


, and



5

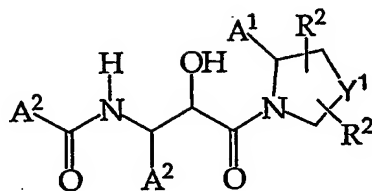
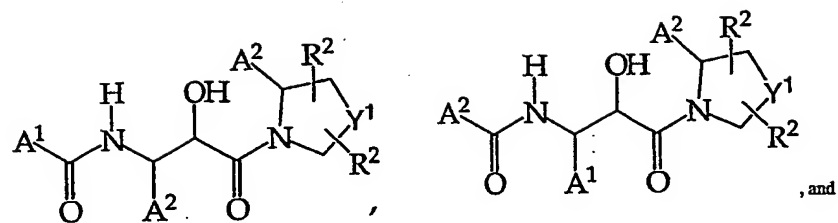
5. A compound of claim 3 selected from:



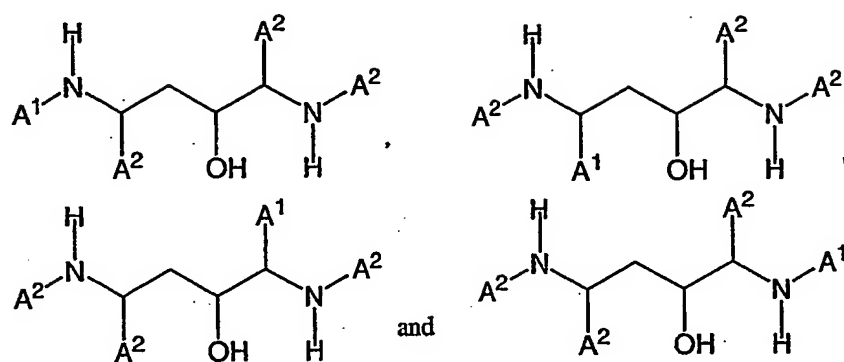
5

6. A compound of claim 3 selected from:

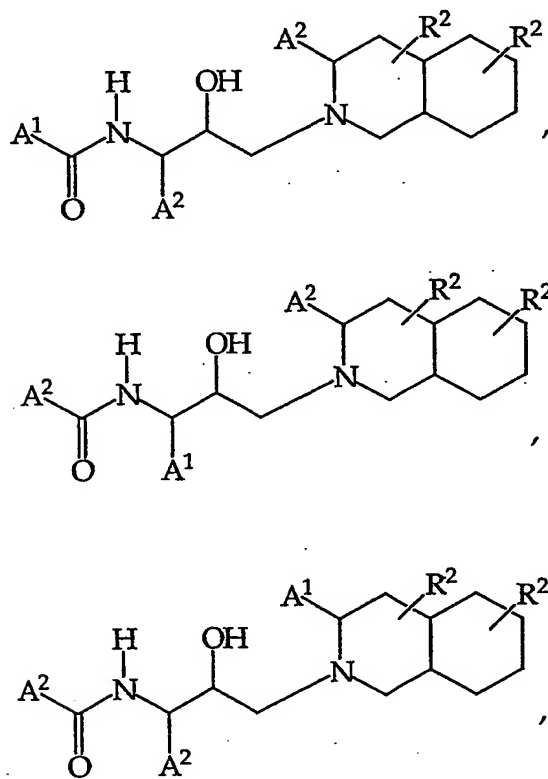


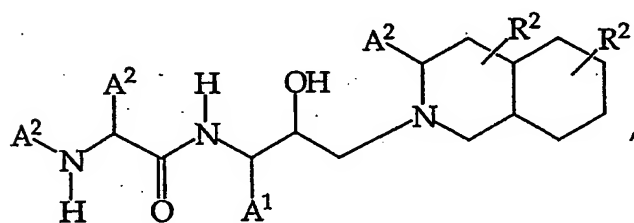
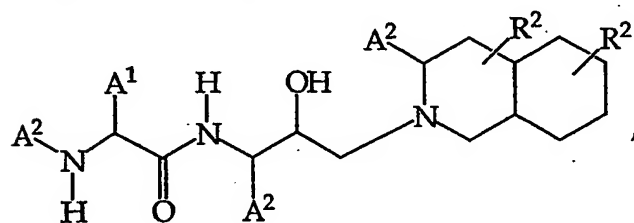
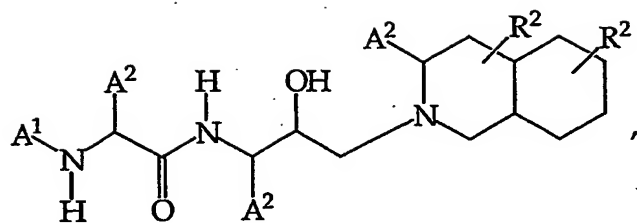


7. A compound of claim 3 selected from:

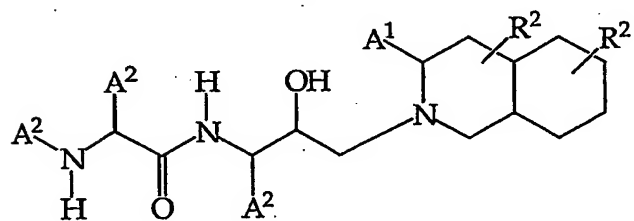


- 5 8. A compound of claim 3 selected from:

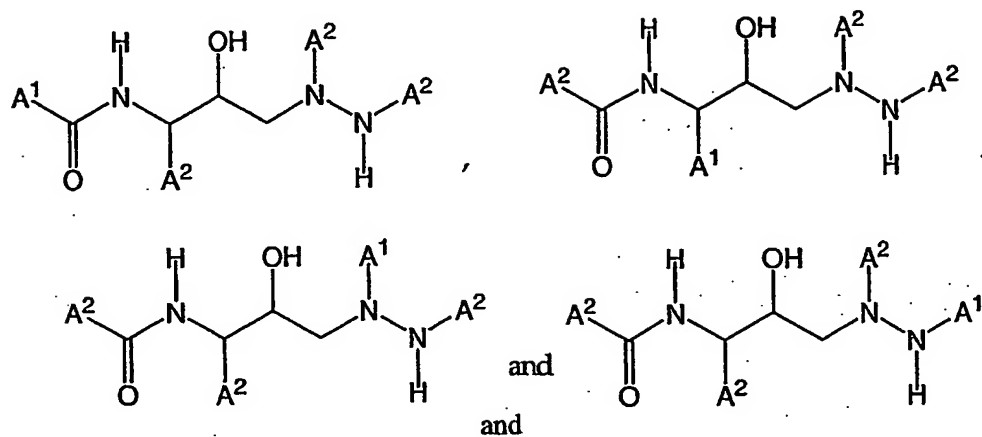




and

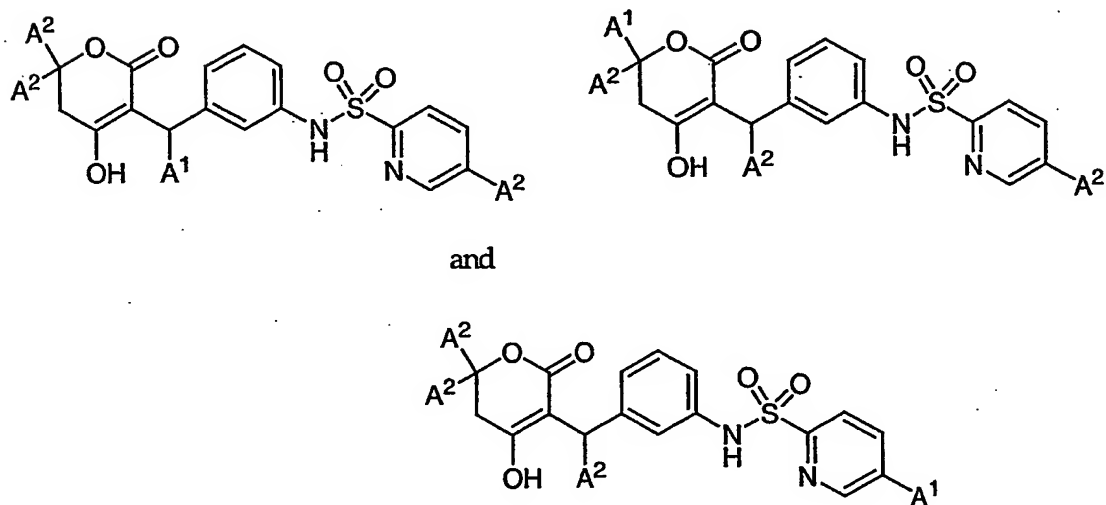


9. A compound of claim 3 selected from:

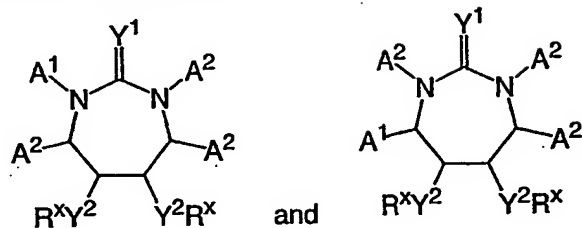


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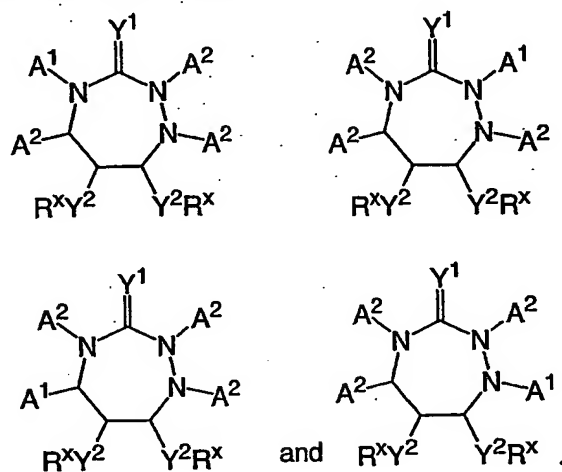
10. A compound of claim 3 selected from:



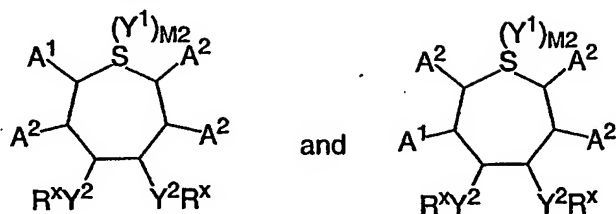
11. A compound of claim 3 selected from:



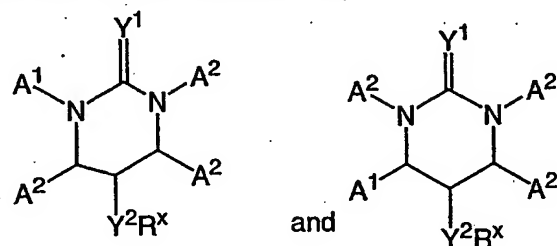
12. A compound of claim 3 selected from:



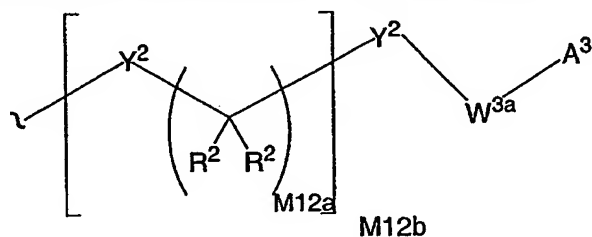
13. A compound of claim 3 selected from:



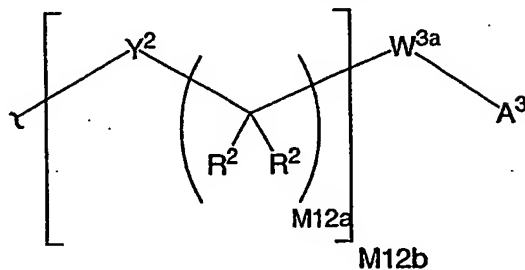
- 5 14. A compound of claim 3 selected from:



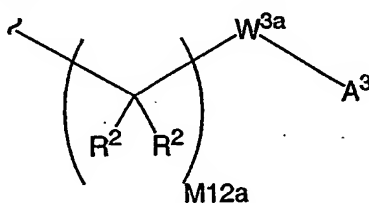
15. A compound of claim 3 wherein  $A^1$  is of the formula:



16. A compound of claim 15 wherein  $A^1$  is of the formula:

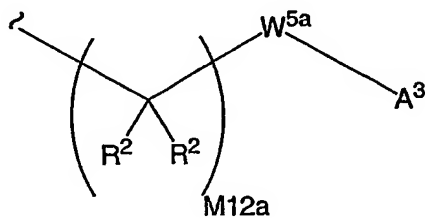


17. A compound of claim 16 wherein  $A^1$  is of the formula:



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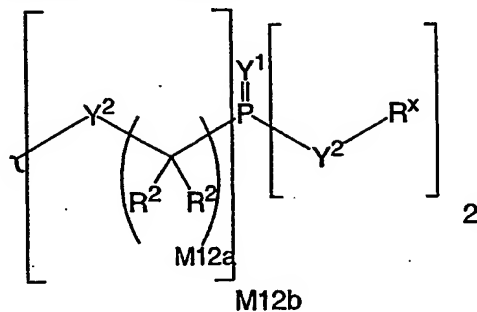
18. A compound of claim 17 wherein  $A^1$  is of the formula:



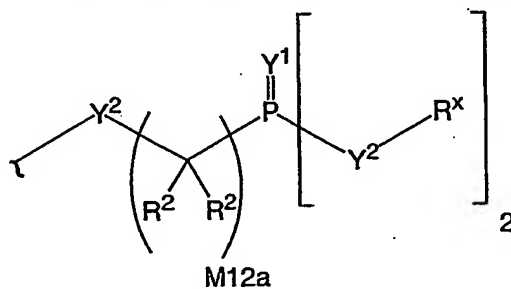
10 and  $W^{5a}$  is a carbocycle or a heterocycle where  $W^{5a}$  is independently substituted with 0 or 1  $R^2$  groups.

19. A compound of claim 18 wherein M12a is 1.

20. A compound of claim 3 wherein  $A^3$  is of the formula:

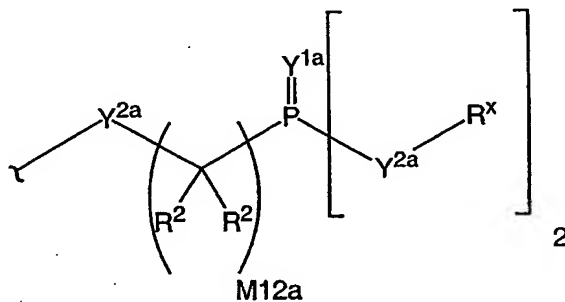


21. A compound of claim 20 wherein  $A^3$  is of the formula:



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22. The compound of claim 21 wherein  $A^3$  is of the formula:



;

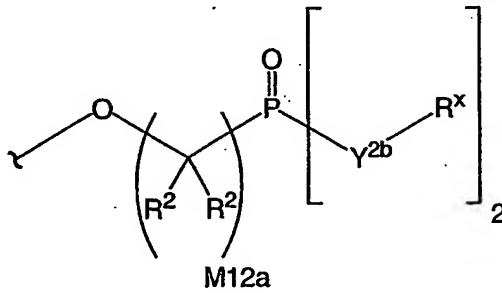
$Y^{1a}$  is O or S; and

$Y^{2a}$  is O,  $N(R^x)$  or S.

10

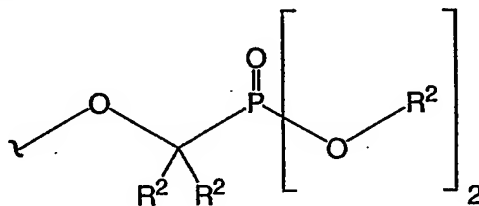


23. The compound of claim 22 wherein  $A^3$  is of the formula:

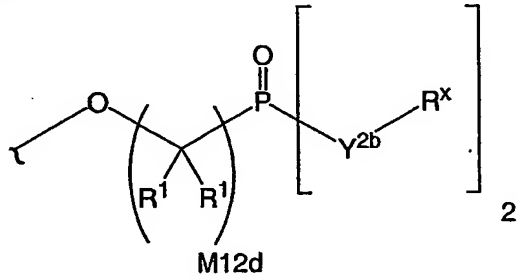


and  $Y^{2b}$  is O or  $N(R^x)$ .

- 5 24. The compound of claim 23 wherein  $A^3$  is of the formula:



25. The compound of claim 23 wherein  $A^3$  is of the formula:



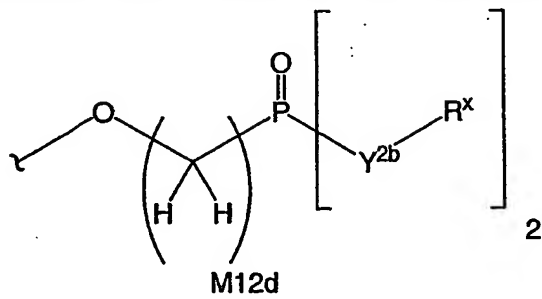
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$R^1$  is independently H or alkyl of 1 to 18 carbon atoms;

$Y^{2b}$  is O or  $N(R^x)$ ; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

26. The compound of claim 25 wherein  $A^3$  is of the formula:



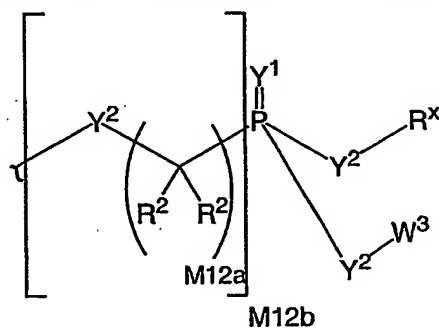
$Y^{2b}$  is O or  $N(R^x)$ ; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

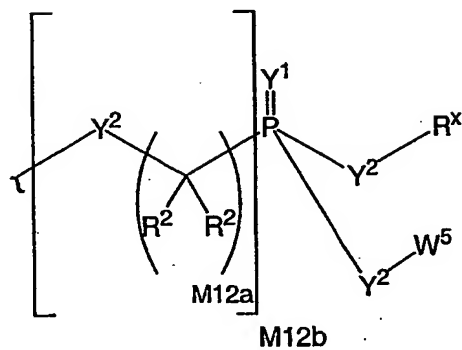
5

27. The compound of claim 26 wherein M12d is 1.

28. The compound of claim 3 wherein  $A^3$  is of the formula:

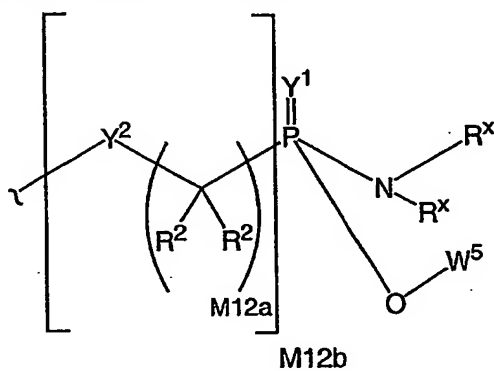


29. The compound of claim 28 wherein  $A^3$  is of the formula:



- 5 30. The compound of claim 29 wherein  $W^5$  is a carbocycle.

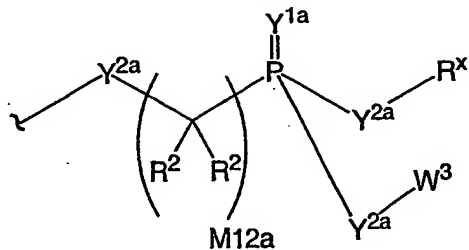
31. The compound of claim 30 wherein  $A^3$  is of the formula:



- 10 32. The compound of claim 31 wherein  $W^5$  is phenyl.

33. The compound of claim 28 wherein M12b is 1.

34. The compound of claim 33 wherein  $A^3$  is of the formula:

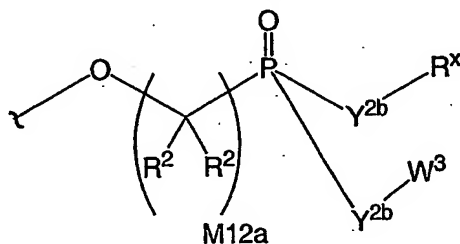


$Y^{1a}$  is O or S; and

$Y^{2a}$  is O,  $N(R^x)$  or S.

5

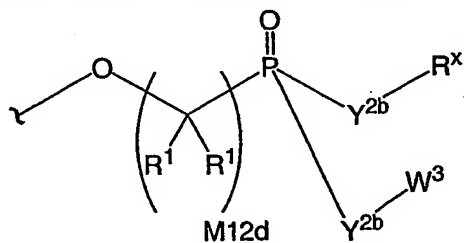
35. The compound of claim 34 wherein  $A^3$  is of the formula:



and  $Y^{2b}$  is O or  $N(R^x)$ .

10

36. The compound of claim 35 wherein  $A^3$  is of the formula:



$R^1$  is independently H or alkyl of 1 to 18 carbon atoms;

$Y^{2b}$  is O or  $N(R^x)$ ; and

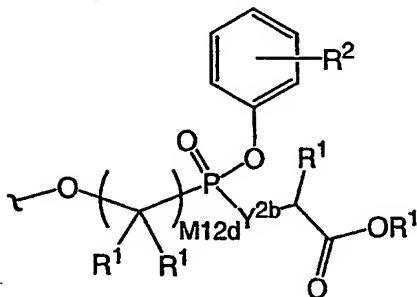
M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

15

37. The compound of claim 36 wherein  $R^1$  is H.

38. The compound of claim 36 wherein M12d is 1.

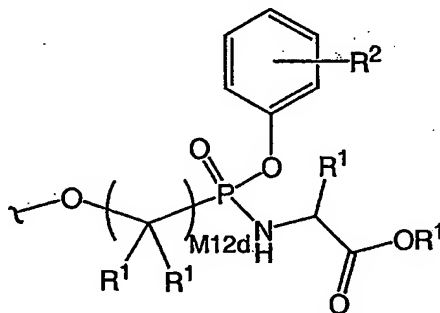
39. The compound of claim 36 wherein  $A^3$  is of the formula:



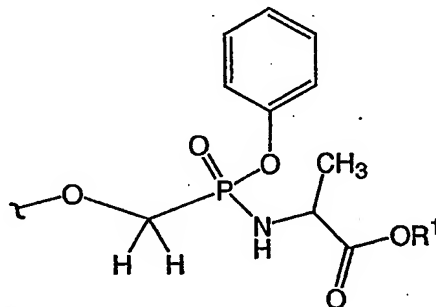
wherein the phenyl carbocycle is substituted with 0 to 3  $R^2$  groups.

5

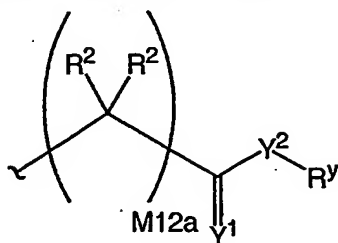
40. The compound of claim 39 wherein  $A^3$  is of the formula:



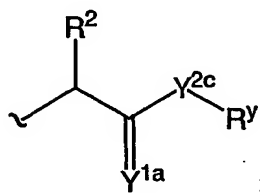
41. The compound of claim 40 wherein  $A^3$  is of the formula:



42. A compound of claim 3 wherein  $R^x$  is of the formula:



43. A compound of claim 42 wherein  $R^x$  is of the formula:

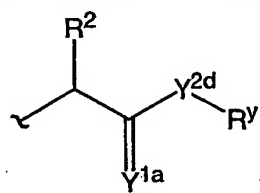


5

$Y^{1a}$  is O or S; and

$Y^{2c}$  is O, N( $R^y$ ) or S.

44. A compound of claim 43 wherein  $R^x$  is of the formula:

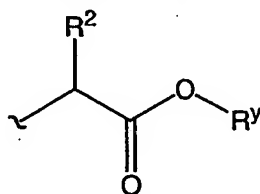


10

$Y^{1a}$  is O or S; and

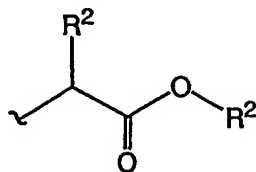
$Y^{2d}$  is O or N( $R^y$ ).

45. A compound of claim 44 wherein  $R^x$  is of the formula:

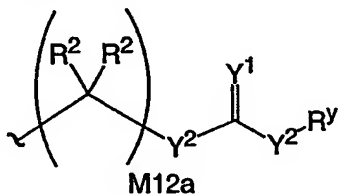


15

46. A compound of claim 45 wherein  $R^x$  is of the formula:

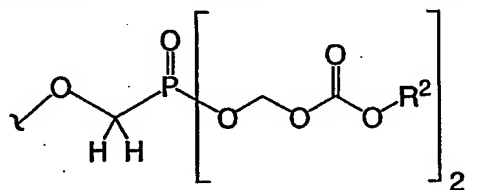


47. The compound of claim 3 wherein  $R^x$  is of the formula:



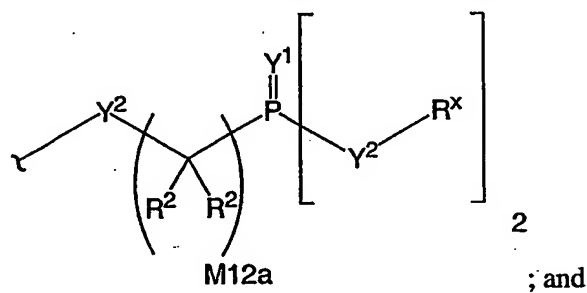
5

48. The compound of claim 47 wherein  $A^3$  is of the formula:

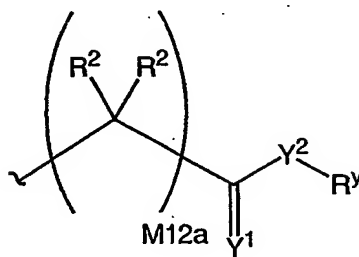


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49. The compound of claim 3 wherein  $A^3$  is of the formula:



$R^x$  is of the formula:



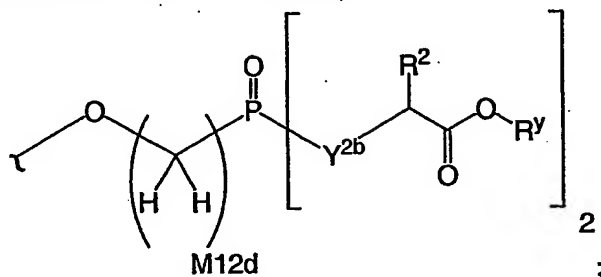




$Y^{2d}$  is O or  $N(R^y)$ ; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

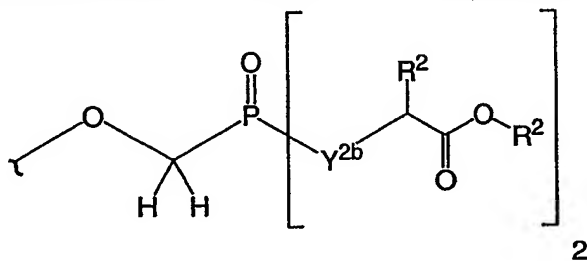
53. The compound of claim 52 wherein  $A^3$  is of the formula:



$Y^{2b}$  is O or  $N(R^2)$ ; and

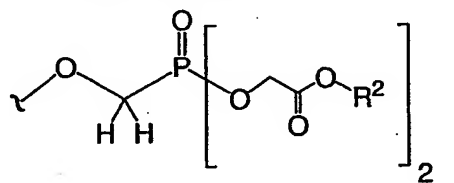
M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

54. The compound of claim 53 wherein  $A^3$  is of the formula:

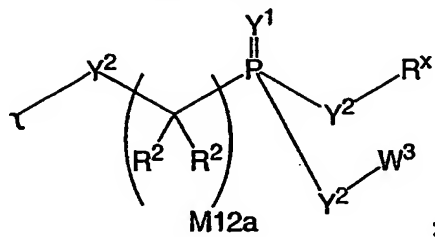


and  $Y^{2b}$  is O or  $N(R^2)$ .

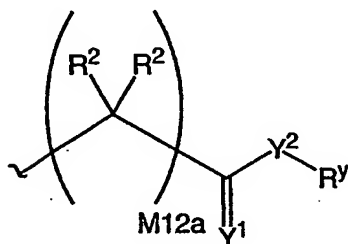
55. The compound of claim 54 wherein  $A^3$  is of the formula:



56. The compound of claim 3 wherein  $A^3$  is of the formula:

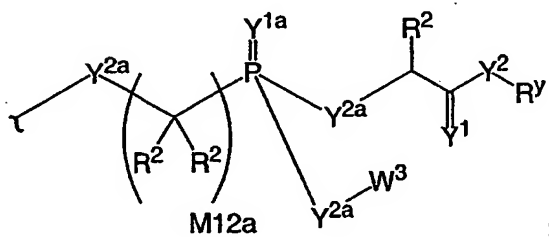


$R^x$  is of the formula:



5

57. The compound of claim 56 wherein  $A^3$  is of the formula:

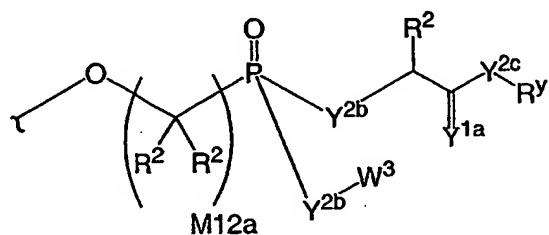


$Y^{1a}$  is O or S; and

10

$Y^{2a}$  is O,  $N(R^2)$  or S.

58. The compound of claim 57 wherein  $A^3$  is of the formula:



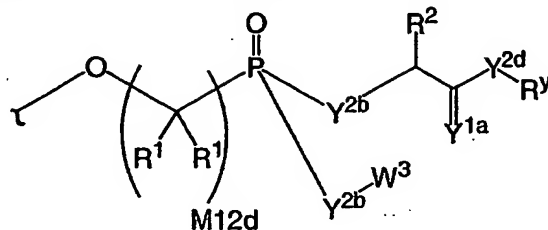
15

$Y^{1a}$  is O or S;

$Y^{2b}$  is O or  $N(R^2)$ ; and

$Y^{2c}$  is O, N(R<sup>y</sup>) or S.

59. The compound of claim 58 wherein A<sup>3</sup> is of the formula:



5

R<sup>1</sup> is independently H or alkyl of 1 to 18 carbon atoms;

Y<sup>1a</sup> is O or S;

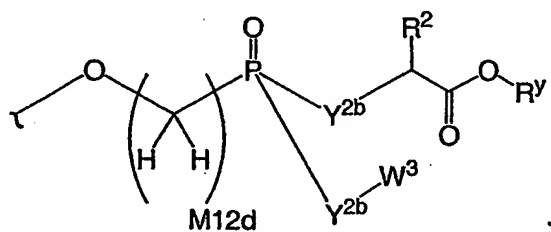
Y<sup>2b</sup> is O or N(R<sup>2</sup>);

Y<sup>2d</sup> is O or N(R<sup>y</sup>); and

10

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

60. The compound of claim 59 wherein A<sup>3</sup> is of the formula:

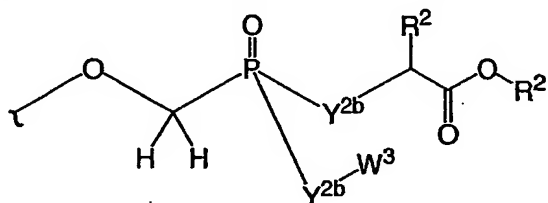


Y<sup>2b</sup> is O or N(R<sup>2</sup>); and

15

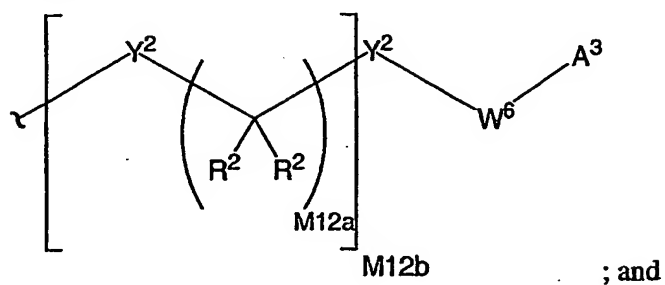
M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

61. The compound of claim 60 wherein A<sup>3</sup> is of the formula:

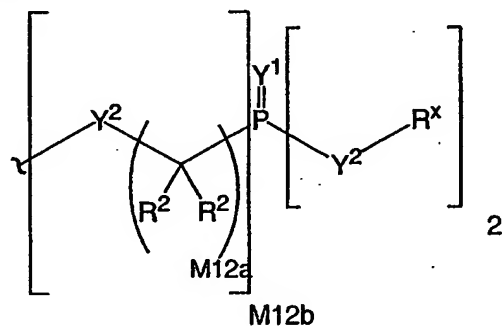


and Y<sup>2b</sup> is O or N(R<sup>2</sup>).

62. The compound of claim 3 wherein  $A^1$  is of the formula:

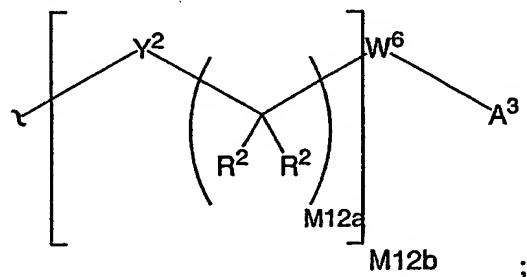


$A^3$  is of the formula:

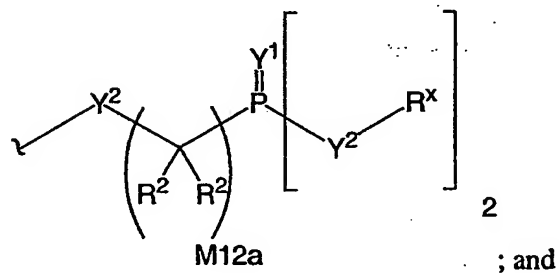


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63. The compound of claim 62 wherein  $A^1$  is of the formula:

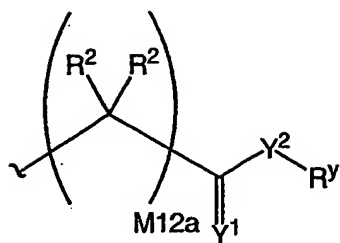


$A^3$  is of the formula:

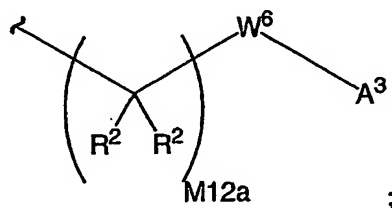


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$R^x$  is of the formula:

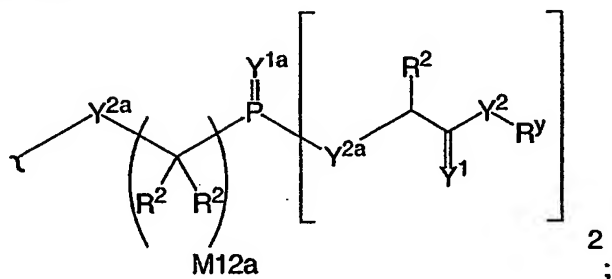


64. The compound of claim 63 wherein  $A^1$  is of the formula:



5

$A^3$  is of the formula:

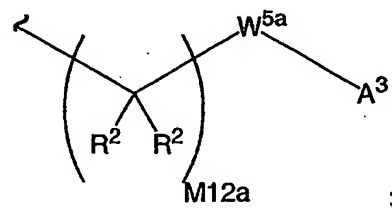


$Y^{1a}$  is O or S; and

$Y^{2a}$  is O, N(R²) or S.

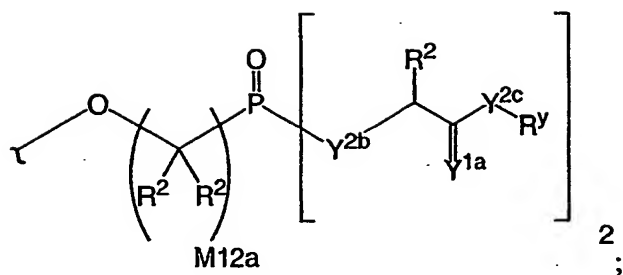
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65. The compound of claim 64 wherein  $A^1$  is of the formula:



$W^{5a}$  is a carbocycle independently substituted with 0 or 1  $R^2$  groups;

$A^3$  is of the formula:



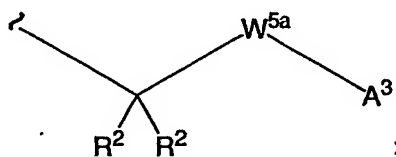
$Y^{1a}$  is O or S;

$Y^{2b}$  is O or  $N(R^2)$ ; and

$Y^{2c}$  is O,  $N(R^y)$  or S.

5

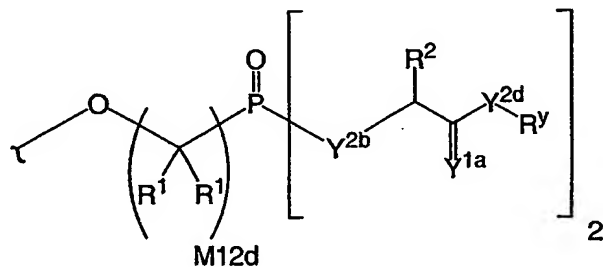
66. The compound of claim 65 wherein  $A^1$  is of the formula:



$W^{5a}$  is a carbocycle independently substituted with 0 or 1  $R^2$  groups;

$A^3$  is of the formula:

10



$R^1$  is independently H or alkyl of 1 to 18 carbon atoms;

$Y^{1a}$  is O or S;

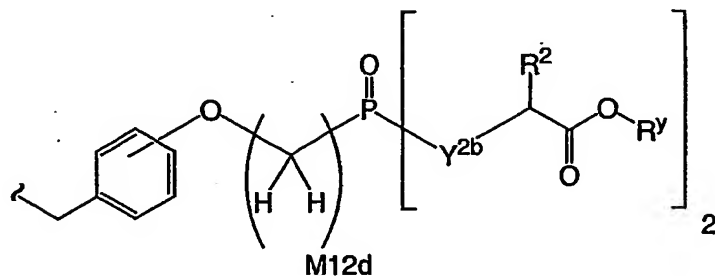
$Y^{2b}$  is O or  $N(R^2)$ ;

$Y^{2d}$  is O or  $N(R^y)$ ; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

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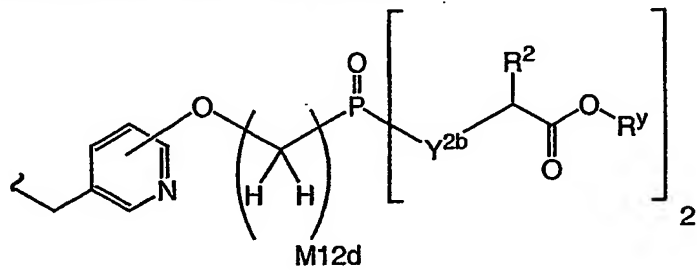
67. The compound of claim 66 wherein  $A^1$  is of the formula:



$Y^{2b}$  is O or  $N(R^2)$ ; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

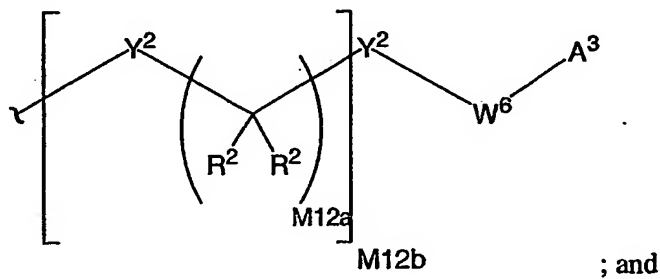
68. The compound of claim 66 wherein  $A^1$  is of the formula:



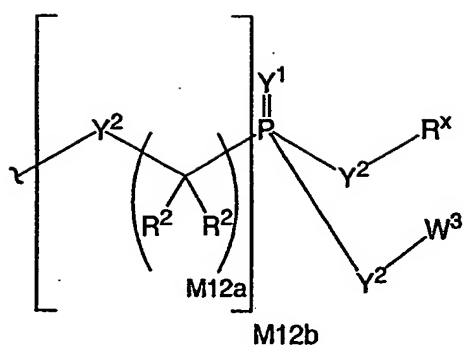
and  $Y^{2b}$  is O or  $N(R^2)$ ; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

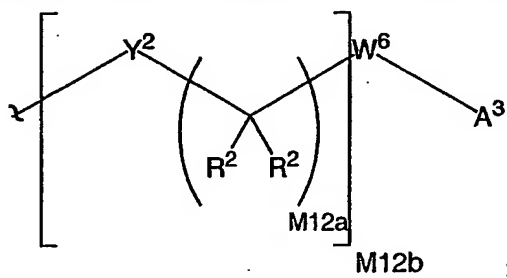
69. The compound of claim 3 wherein  $A^1$  is of the formula:



$A^3$  is of the formula:

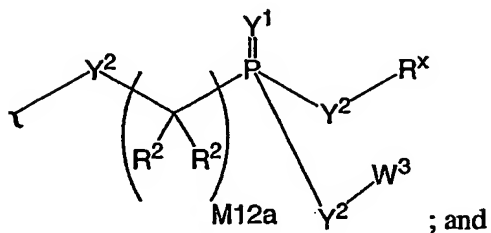


70. The compound of claim 69 wherein  $A^1$  is of the formula:

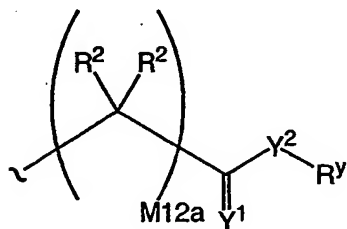


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$A^3$  is of the formula:



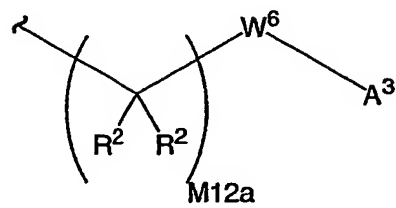
$R^x$  is of the formula:



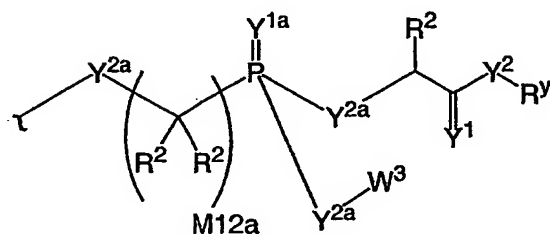
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71. The compound of claim 70 wherein  $A^1$  is of the formula:



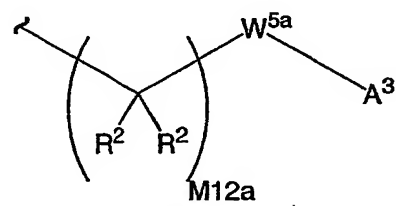
$A^3$  is of the formula:



$Y^{1a}$  is O or S; and

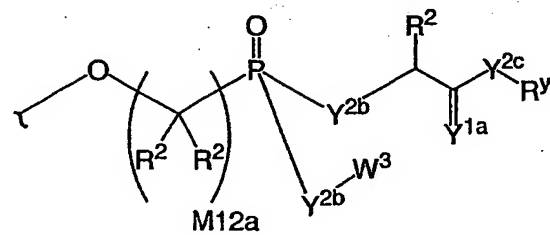
$Y^{2a}$  is O, N( $R^2$ ) or S.

72. The compound of claim 71 wherein  $A^1$  is of the formula:



$W^{5a}$  is a carbocycle independently substituted with 0 or 1  $R^2$  groups;

$A^3$  is of the formula:

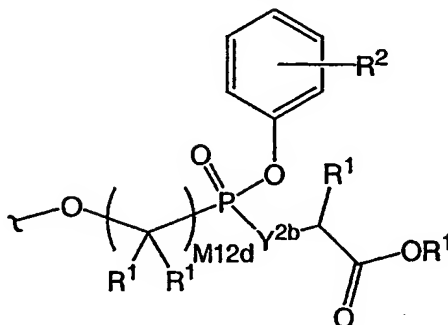


$Y^{1a}$  is O or S;

$Y^{2b}$  is O or N( $R^2$ ); and

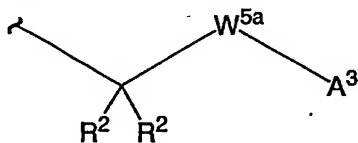
$Y^{2c}$  is O, N( $R^y$ ) or S.

73. The compound of claim 72 wherein  $A^3$  is of the formula:



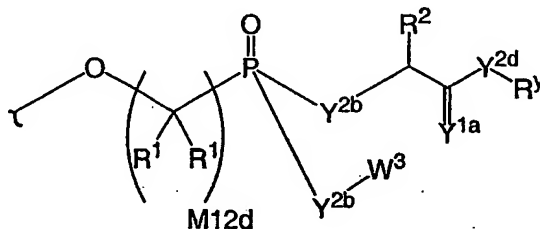
wherein  $R^1$  is independently H or alkyl of 1 to 18 carbon atoms; and the phenyl carbocycle is substituted with 0 to 3  $R^2$  groups.

74. The compound of claim 70 wherein  $A^1$  is of the formula:



$W^{5a}$  is a carbocycle or heterocycle where  $W^{5a}$  is independently substituted with 0 or 1  $R^2$  groups;

$A^3$  is of the formula:



$Y^{1a}$  is O or S;

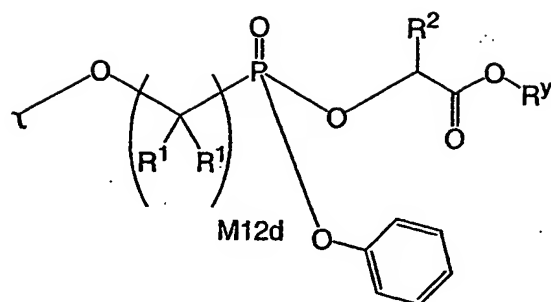
$Y^{2b}$  is O or  $N(R^2)$ ;

$Y^{2d}$  is O or  $N(R^y)$ ; and

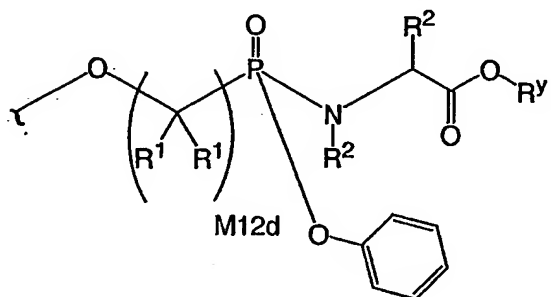
M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

75. A compound of claim 74 wherein  $Y^{2b}$  is O and  $W^3$  is phenyl.

76. A compound of claim 75 wherein  $A^3$  is of the formula:

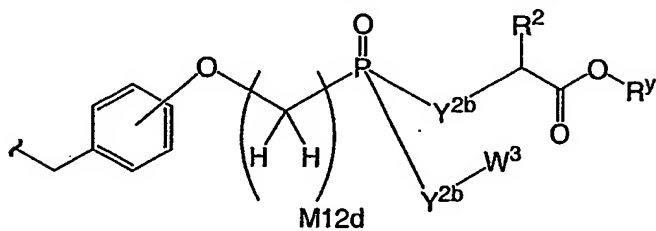


77. A compound of claim 75 wherein A<sup>3</sup> is of the formula:



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78. A compound of claim 74 wherein A<sup>1</sup> is of the formula:

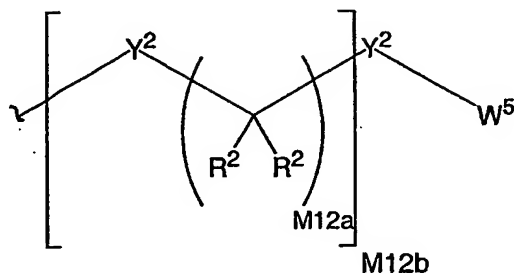


Y<sup>2b</sup> is O or N(R<sup>2</sup>); and

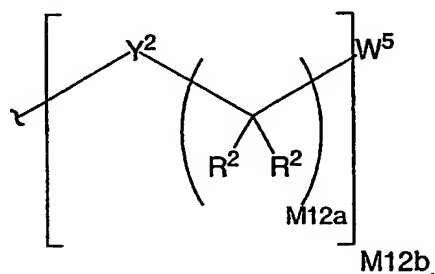
M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

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79. The compound of claim 3 wherein  $A^2$  is of the formula:



80. The compound of claim 79 wherein  $A^2$  is of the formula:

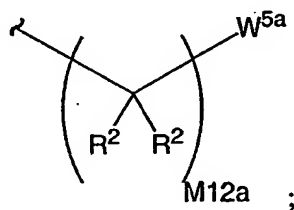


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81. The compound of claim 80 wherein M12b is 1.

82. The compound of claim 80 where M12b is 0,  $Y^2$  is a bond and  $W^5$  is a carbocycle or heterocycle where  $W^5$  is optionally and independently substituted with 1, 2, or 3  $R^2$  groups.

83. The compound of claim 80 wherein  $A^2$  is of the formula:



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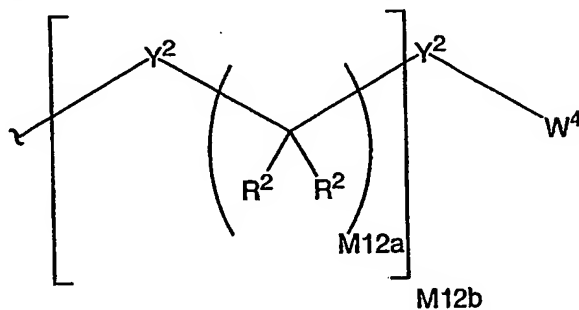
and  $W^{5a}$  is a carbocycle or heterocycle where  $W^{5a}$  is optionally and independently substituted with 1, 2, or 3  $R^2$  groups.

84. The compound of claim 83 wherein M12a is 1.

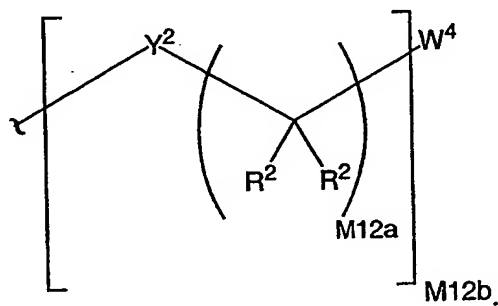
85. The compound of claim 83 wherein A<sup>2</sup> is selected from phenyl, substituted phenyl, benzyl, substituted benzyl, pyridyl and substituted pyridyl.

5

86. The compound of claim 3 wherein A<sup>2</sup> is of the formula:



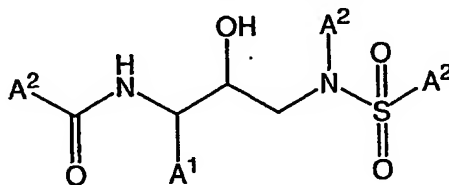
87. The compound of claim 86 wherein A<sup>2</sup> is of the formula:



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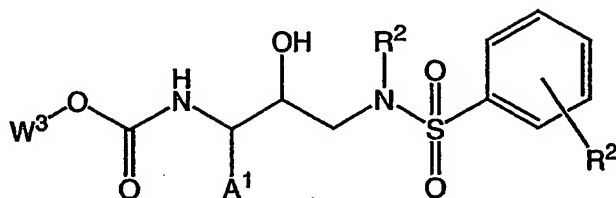
88. The compound of claim 87 wherein M12b is 1.

89. A Formula II compound of claim 5 having the formula:

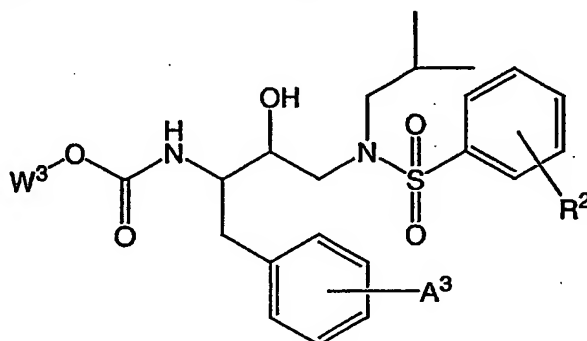


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90. A compound of claim 89 having the formula:



91. A compound of claim 90 having the formula:

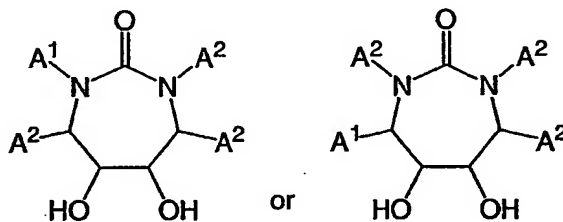


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92. A compound of the formula MBF.

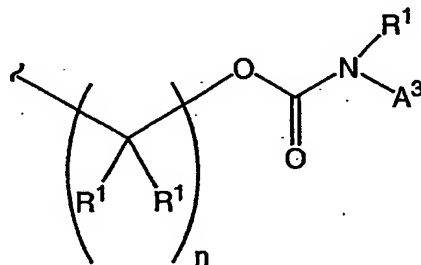
93. A compound of claim 92 having the formula:

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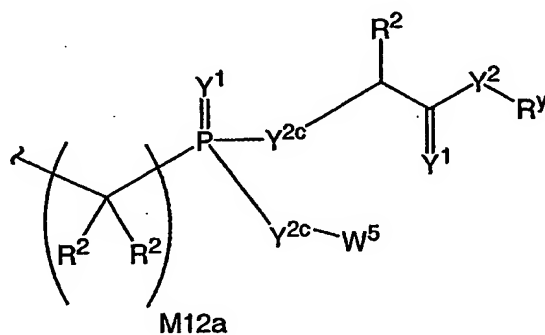


94. The compound of claim 93 wherein A<sup>2</sup> is selected from benzyl, substituted benzyl, heterocycle and substituted heterocycle.

95. A compound of claim 3 wherein  $A^1$  is of the formula:



$R^1$  is independently H or alkyl of 1 to 18 carbon atoms; and  $n$  is an integer from 1 to 18;  $A^3$  is of the formula:



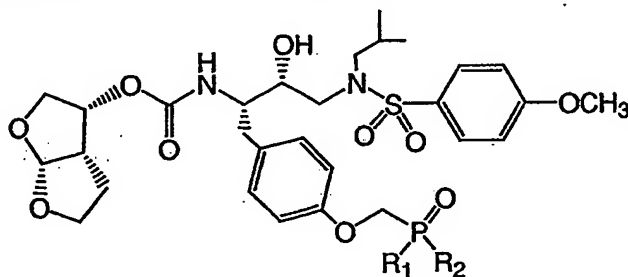
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and  $Y^{2c}$  is O,  $N(R^y)$  or S.

96. The compound of claim 95 wherein  $R^1$  is H and  $n$  is 1.

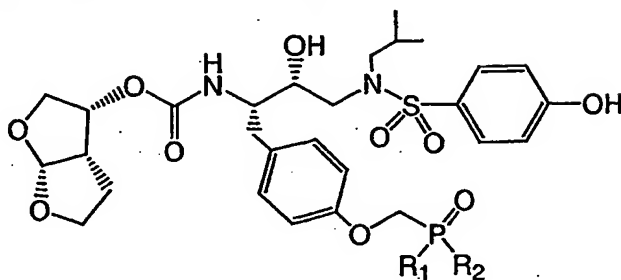
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97. A compound of claim 91 having the formula:



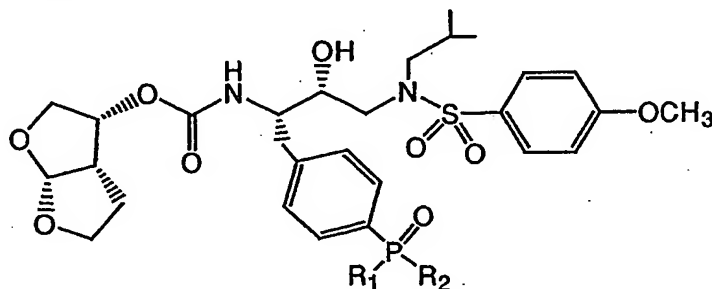
wherein  $R_1$  and  $R_2$  are independently selected from hydroxy, methoxy, ethoxy, trifluoroethoxy, isopropoxy, phenoxy, benzyloxy, and O-pivaloyloxymethyl.

98. A compound of claim 91 having the formula:



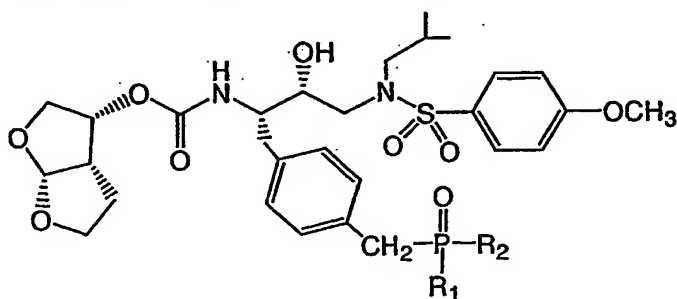
wherein  $R_1$  and  $R_2$  are independently selected from hydroxy, methoxy, ethoxy,  
5 trifluoroethoxy, isopropoxy, phenoxy, benzyloxy, and O-pivaloyloxymethyl.

99. A compound of claim 91 having the formula:



10 wherein  $R_1$  and  $R_2$  are independently selected from hydroxy, methoxy, ethoxy,  
trifluoroethoxy, isopropoxy, phenoxy, benzyloxy, and O-pivaloyloxymethyl.

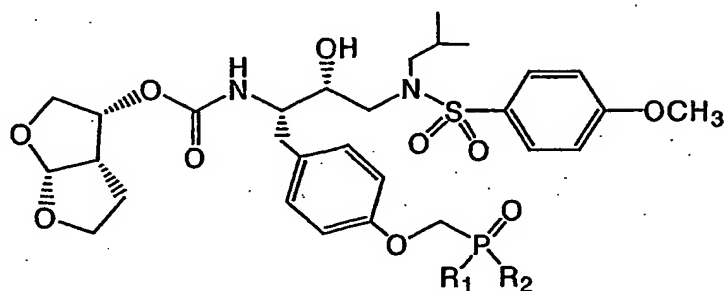
100. A compound of claim 91 having the formula:



15 wherein  $R_1$  and  $R_2$  are independently selected from hydroxy, methoxy, ethoxy,  
trifluoroethoxy, isopropoxy, phenoxy, benzyloxy, and O-pivaloyloxymethyl.



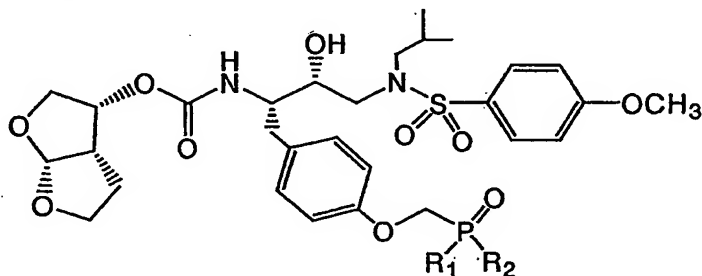
101. A compound of claim 91 having the formula:



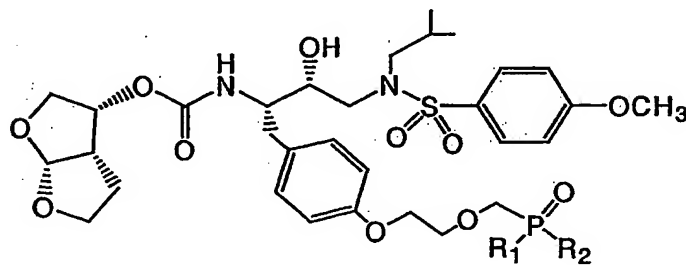
5 wherein  $R_1$  and  $R_2$  are independently selected from  $-NR$  where  $R$  is  $C_1-C_6$  alkyl or an amino acid ester.

102. The compound of claim 101 wherein  $R_1$  and  $R_2$  are independently selected from  $-NMe$ ,  $-NEt$ , Gly-Et, Ala-Et, Aba-Et, Val-Et, Leu-Et, Phe-Bu, and Phe-Et.

10 103. A compound of claim 91 having the formula:



or



15 wherein  $R_1$  and  $R_2$  are independently selected from hydroxy, methoxy, ethoxy, trifluoroethoxy, isopropoxy, phenoxy, benzyloxy, *O*-pivaloyloxymethyl, and a lactate ester.

104. The compound of claim 103 wherein  $R_1$  is hydroxy, methoxy, ethoxy, trifluoroethoxy, isopropoxy, phenoxy, substituted phenoxy or benzyloxy; and  $R_2$  is Glc-Et, Lac-Me, Lac-Et, Lac-iPr, Lac-Bu, Lac-EtMor, Lac-Me, Lac-Et, Lac-Bn, Lac-Bn, Lac-OH, Lac-OH, Hba-Et, Hba-tBu, Hba-OH, MeBut-Et, or DiMePro-Me.

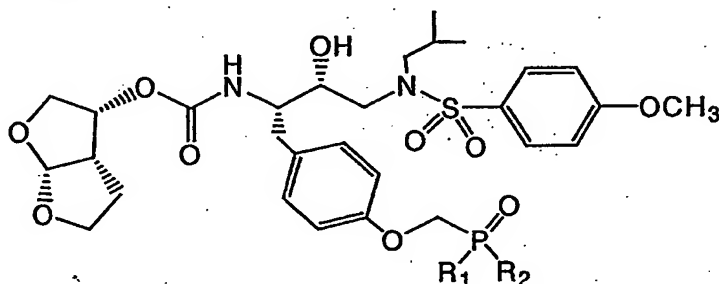
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105. A compound of claim 104 where the lactate ester is the (R) configuration.

106. A compound of claim 104 where the lactate ester is the (S) configuration.

10

107. A compound of claim 91 having the formula:

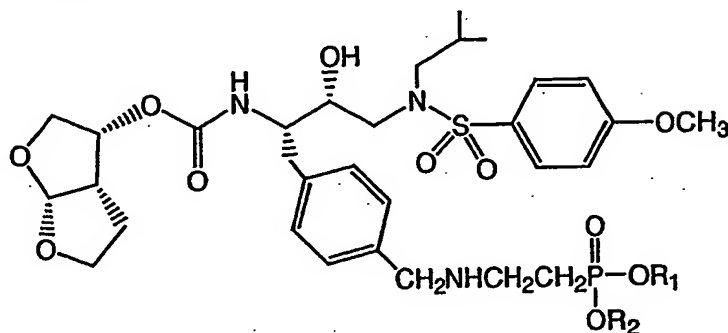


wherein  $R_1$  is phenoxy, benzyloxy, ethoxy, trifluoroethoxy, or hydroxyl; and  $R_2$  is an amino acid ester.

15

108. The compound of claim 107 wherein the amino acid ester is selected from Gly-Bu, Ala-Me, Ala-Et, Ala-iPr, (D)Ala-iPr, Ala-Bu, Aba-Et, Aba-Bu, and Ala-OH.

109. A compound of claim 91 having the formula:

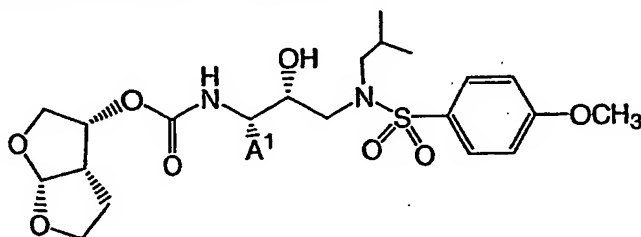


wherein  $R_1$  and  $R_2$  are independently selected from hydroxy, methoxy, ethoxy,  
 5 trifluoroethoxy, isopropoxy, phenoxy, benzyloxy, O-pivaloyloxymethyl, an amino acid ester  
 and a lactate ester.

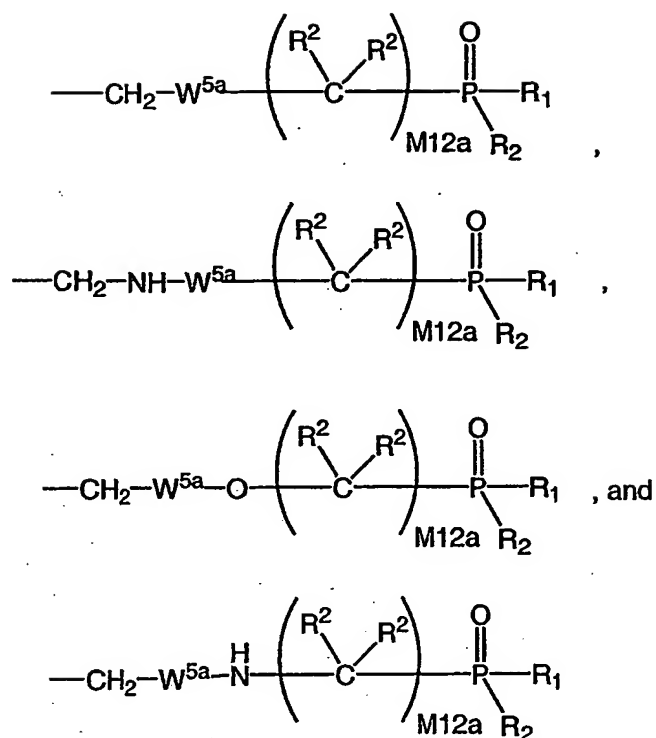
110. The compound of claim 109 wherein  $R_1$  is hydroxy, methoxy, ethoxy,  
 trifluoroethoxy, isopropoxy, phenoxy, substituted phenoxy or benzyloxy; and  $R_2$  is a lactate  
 10 ester selected from Glc-Et, Lac-Me, Lac-Et, Lac-iPr, Lac-Bu, Lac-EtMor, Lac-Me, Lac-Et,  
 Lac-Bn, Lac-Bn, Lac-OH, Lac-OH, Hba-Et, Hba-tBu, Hba-OH, MeBut-Et, and DiMePro-  
 Me.

111. The compound of claim 109 wherein  $R_1$  is hydroxy, methoxy, ethoxy,  
 15 trifluoroethoxy, isopropoxy, phenoxy, substituted phenoxy or benzyloxy; and  $R_2$  is an amino  
 acid ester is selected from Gly-Bu, Ala-Me, Ala-Et, Ala-iPr, (D)Ala-iPr, Ala-Bu, Aba-Et,  
 Aba-Bu, and Ala-OH.

112. A compound of claim 5 having the formula:

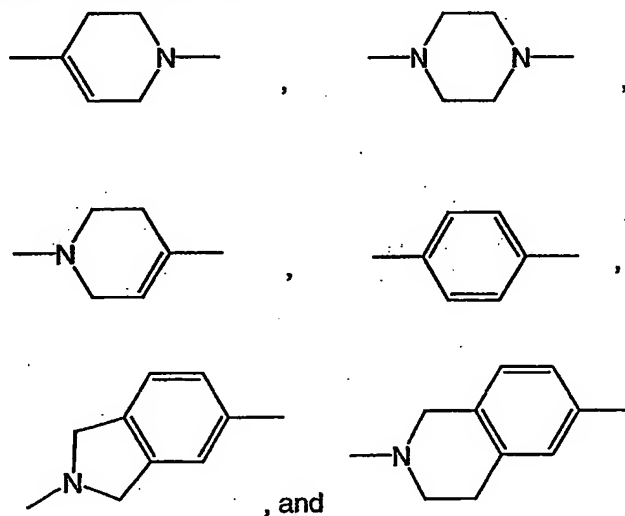


wherein  $A^1$  is selected from the formulas:

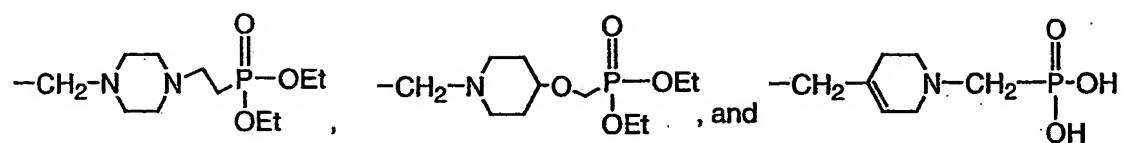


$\text{R}_1$  and  $\text{R}_2$  are independently selected from hydroxy, methoxy, ethoxy, trifluoroethoxy, isopropoxy, phenoxy, benzyloxy, O-pivaloyloxymethyl, an amino acid ester and a lactate ester; and

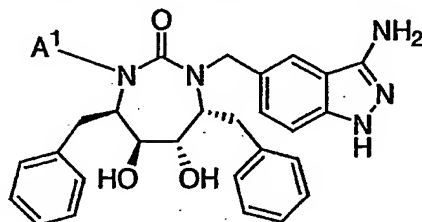
5  $\text{W}^{5a}$  is selected from the formulas:



113. A compound of claim 112 wherein  $\text{A}^1$  is selected from the formulas:

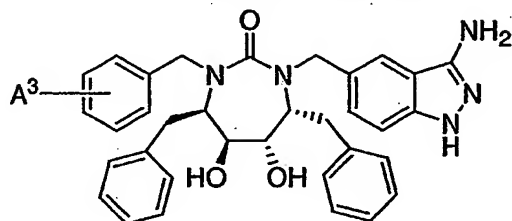


114. A compound of claim 94 having the structure:



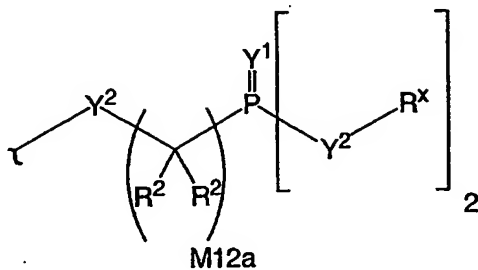
5

115. A compound of claim 114 having the structure:

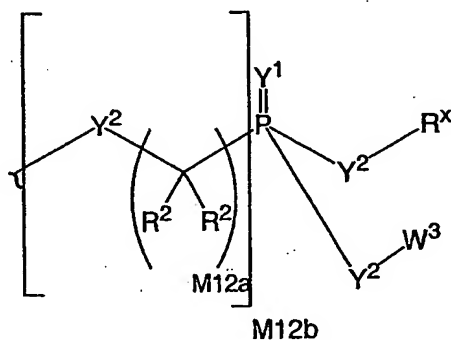


wherein the ortho, meta, or para carbon of the phenyl ring is substituted with A<sup>3</sup>.

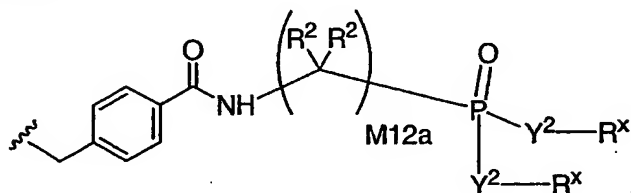
116. A compound of claim 115 wherein  $A^3$  is of the formula:



117. A compound of claim 115 wherein  $A^3$  is of the formula:

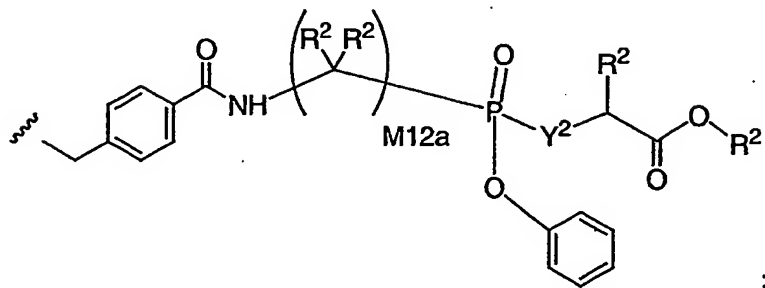


118. A compound of claim 114 wherein  $A^1$  is of the formula:



119. A compound of claim 118 wherein  $Y^2$  is O,  $R^2$  is H, and  $R^x$  is  $C_1$ - $C_6$  alkyl.

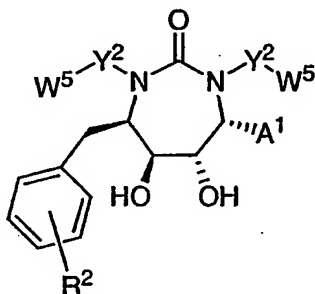
120. A compound of claim 118 wherein A<sup>1</sup> is of the formula:



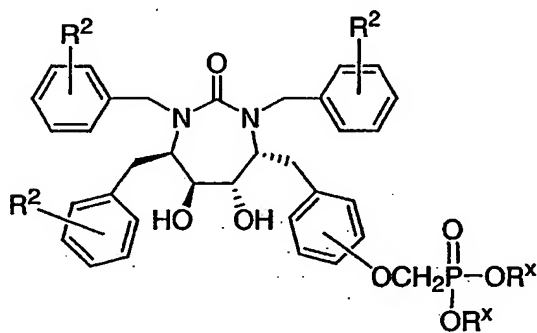
and Y<sup>2</sup> is O, NH, or NR<sup>4</sup>.

5

121. A Formula VIIIa compound of claim 3 having the structure:

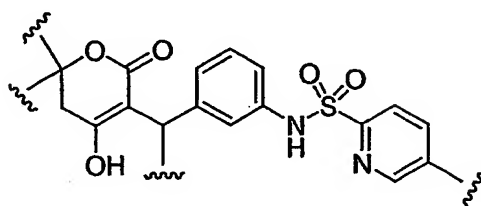
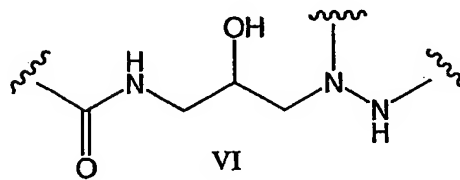
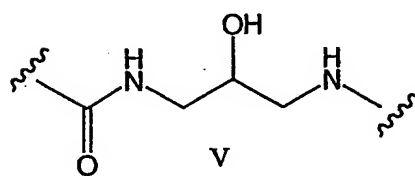
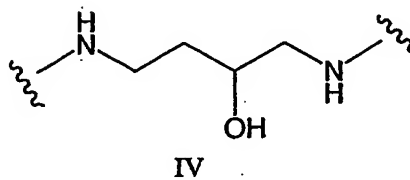
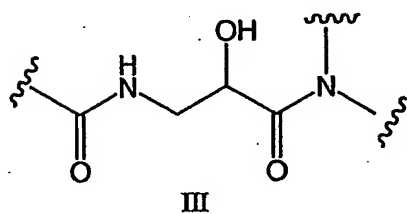
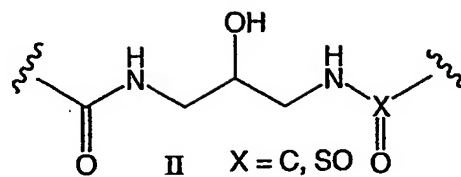
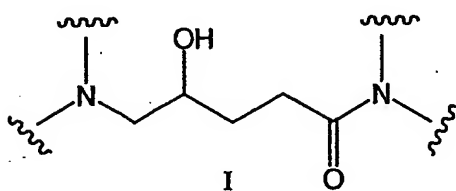


122. A Formula VIIIa compound of claim 3 having the structure:

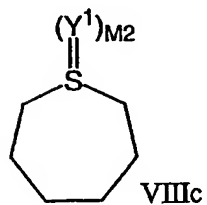
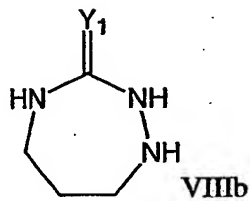
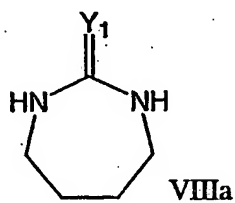


10

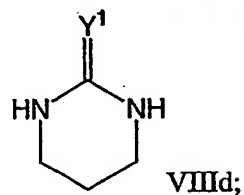
123. A compound selected from the Formulas:



5



and



10



wherein Formulas I, II, III, IV, V, VI, VII and VIIIa-d are substituted with one or more covalently attached A<sub>1</sub> groups, and optionally substituted with one or more covalently attached A<sub>2</sub> groups;

A<sub>1</sub> is -(X<sub>2</sub>-(C(R<sub>2</sub>)(R<sub>2</sub>))<sub>m1</sub>-X<sub>3</sub>)<sub>m1</sub>-W<sub>3</sub>, wherein W<sub>3</sub> is substituted with 1 to 3 A<sub>3</sub>

5 groups;

A<sub>2</sub> is -(X<sub>2</sub>-(C(R<sub>2</sub>)(R<sub>2</sub>))<sub>m1</sub>-X<sub>3</sub>)<sub>m1</sub>-W<sub>3</sub>;

A<sub>3</sub> is -(X<sub>2</sub>-(C(R<sub>2</sub>)(R<sub>2</sub>))<sub>m1</sub>-X<sub>3</sub>)<sub>m1</sub>-P(Y<sub>1</sub>)(Y<sub>1</sub>R<sub>6a</sub>)(Y<sub>1</sub>R<sub>6a</sub>);

X<sub>2</sub> and X<sub>3</sub> are independently a bond, -O-, -N(R<sub>2</sub>)-, -N(OR<sub>2</sub>)-, -N(N(R<sub>2</sub>)(R<sub>2</sub>))- , -S-, -SO-, or -SO<sub>2</sub>-;

10 each Y<sub>1</sub> is independently O, N(R<sub>2</sub>), N(OR<sub>2</sub>), or N(N(R<sub>2</sub>)(R<sub>2</sub>)), wherein each Y<sub>1</sub> is bound by two single bonds or one double bond;

R<sub>1</sub> is independently H or alkyl of 1 to 12 carbon atoms;

R<sub>2</sub> is independently H, R<sub>3</sub> or R<sub>4</sub> wherein each R<sub>4</sub> is independently substituted with 0 to 3 R<sub>3</sub> groups;

15 R<sub>3</sub> is independently F, Cl, Br, I, -CN, N<sub>3</sub>, -NO<sub>2</sub>, -OR<sub>6a</sub>, -OR<sub>1</sub>, -N(R<sub>1</sub>)<sub>2</sub>, -N(R<sub>1</sub>)(R<sub>6b</sub>), -N(R<sub>6b</sub>)<sub>2</sub>, -SR<sub>1</sub>, -SR<sub>6a</sub>, -S(O)R<sub>1</sub>, -S(O)<sub>2</sub>R<sub>1</sub>, -S(O)OR<sub>1</sub>, -S(O)OR<sub>6a</sub>, -S(O)<sub>2</sub>OR<sub>1</sub>, -S(O)<sub>2</sub>OR<sub>6a</sub>, -C(O)OR<sub>1</sub>, -C(O)R<sub>6c</sub>, -C(O)OR<sub>6a</sub>, -OC(O)R<sub>1</sub>, -N(R<sub>1</sub>)(C(O)R<sub>1</sub>), -N(R<sub>6b</sub>)(C(O)R<sub>1</sub>), -N(R<sub>1</sub>)(C(O)OR<sub>1</sub>), -N(R<sub>6b</sub>)(C(O)OR<sub>1</sub>), -C(O)N(R<sub>1</sub>)<sub>2</sub>, -C(O)N(R<sub>6b</sub>)(R<sub>1</sub>), -C(O)N(R<sub>6b</sub>)<sub>2</sub>, -C(NR<sub>1</sub>)(N(R<sub>1</sub>)<sub>2</sub>), -C(N(R<sub>6b</sub>))(N(R<sub>1</sub>)<sub>2</sub>), -C(N(R<sub>1</sub>))(N(R<sub>1</sub>)(R<sub>6b</sub>)), -C(N(R<sub>6b</sub>))(N(R<sub>1</sub>)(R<sub>6b</sub>)), -C(N(R<sub>1</sub>))(N(R<sub>6b</sub>)<sub>2</sub>), -C(N(R<sub>6b</sub>))(N(R<sub>6b</sub>)<sub>2</sub>), -N(R<sub>1</sub>)C(N(R<sub>1</sub>))(N(R<sub>1</sub>)<sub>2</sub>), -N(R<sub>1</sub>)C(N(R<sub>1</sub>))(N(R<sub>1</sub>)(R<sub>6b</sub>)), -N(R<sub>1</sub>)C(N(R<sub>6b</sub>))(N(R<sub>1</sub>)<sub>2</sub>), -N(R<sub>6b</sub>)C(N(R<sub>1</sub>))(N(R<sub>1</sub>)<sub>2</sub>), -N(R<sub>6b</sub>)C(N(R<sub>6b</sub>))(N(R<sub>1</sub>)<sub>2</sub>), -N(R<sub>6b</sub>)C(N(R<sub>1</sub>))(N(R<sub>1</sub>)(R<sub>6b</sub>)), -N(R<sub>1</sub>)C(N(R<sub>6b</sub>))(N(R<sub>1</sub>)(R<sub>6b</sub>)), -N(R<sub>1</sub>)C(N(R<sub>1</sub>))(N(R<sub>6b</sub>)<sub>2</sub>), -N(R<sub>6b</sub>)C(N(R<sub>6b</sub>))(N(R<sub>1</sub>)(R<sub>6b</sub>)), -N(R<sub>6b</sub>)C(N(R<sub>1</sub>))(N(R<sub>6b</sub>)<sub>2</sub>), -N(R<sub>1</sub>)C(N(R<sub>6b</sub>))(N(R<sub>6b</sub>)<sub>2</sub>), =O, =S, =N(R<sub>1</sub>), =N(R<sub>6b</sub>) or W<sub>5</sub>;

R<sub>4</sub> is independently alkyl of 1 to 12 carbon atoms, alkenyl of 2 to 12 carbon atoms, or alkynyl of 2 to 12 carbon atoms;

R<sub>5</sub> is independently R<sub>4</sub> wherein each R<sub>4</sub> is substituted with 0 to 3 R<sub>3</sub> groups; or R<sub>5</sub> is independently alkylene of 1 to 12 carbon atoms, alkenylene of 2 to 12 carbon atoms, or

alkynylene of 2-12 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R<sub>3</sub> groups;

R<sub>6a</sub> is independently H or an ether- or ester-forming group;

5 R<sub>6b</sub> is independently H, a protecting group for amino or the residue of a carboxyl-containing compound;

R<sub>6c</sub> is independently H or the residue of an amino-containing compound;

W<sub>3</sub> is W<sub>4</sub> or W<sub>5</sub>;

W<sub>4</sub> is R<sub>5</sub>, -C(Y<sub>1</sub>)R<sub>5</sub>, -C(Y<sub>1</sub>)W<sub>5</sub>, -SO<sub>2</sub>R<sub>5</sub>, or -SO<sub>2</sub>W<sub>5</sub>;

W<sub>5</sub> is carbocycle or heterocycle wherein W<sub>5</sub> is independently substituted with 0 to 3

10 R<sub>2</sub> groups;

m<sub>1</sub> is independently an integer from 0 to 12, wherein the sum of all m<sub>1</sub>'s within each individual claim of A<sub>1</sub>, A<sub>2</sub> or A<sub>3</sub> is 12 or less;

m<sub>2</sub> is independently an integer from 0 to 2; and

~ indicates a site of covalent attachment of A<sub>1</sub> or A<sub>2</sub>.

15

124. The compound of claim 123 wherein:

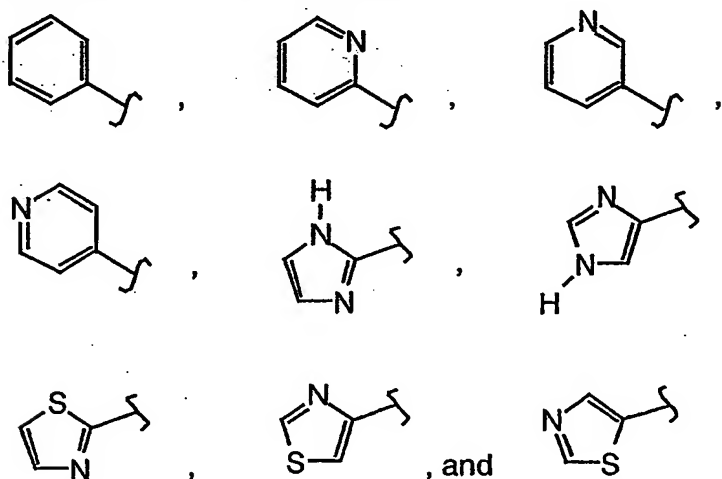
A<sub>1</sub> is -(C(R<sub>2</sub>)(R<sub>2</sub>))<sub>m1</sub>-W<sub>3</sub>, wherein W<sub>3</sub> is substituted with 1 A<sub>3</sub> group;

A<sub>2</sub> is -(C(R<sub>2</sub>)(R<sub>2</sub>))<sub>m1</sub>-W<sub>3</sub>; and

A<sub>3</sub> is -(C(R<sub>2</sub>)(R<sub>2</sub>))<sub>m1</sub>-P(Y<sub>1</sub>)(Y<sub>1</sub>R<sub>6a</sub>)(Y<sub>1</sub>R<sub>6a</sub>).

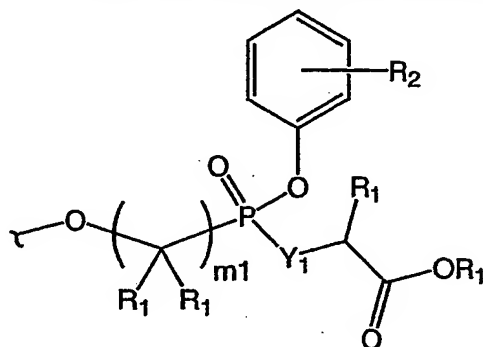
20

125. The compound of claim 123 wherein W<sub>3</sub> is W<sub>5</sub>, and W<sub>5</sub> is selected from:



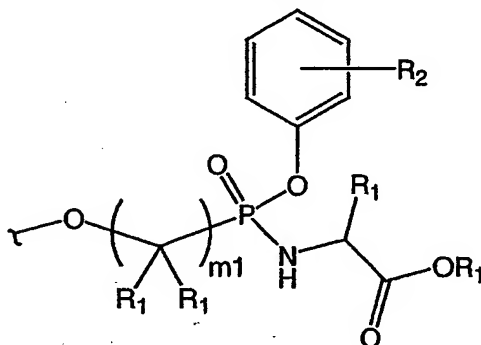
126. The compound of claim 125 wherein  $W_5$  is a pyridine heterocycle bonded to  $-C(R_2)_2-$  at the 2, 3, 4, 5 or 6 position.

5 127. The compound of claim 125 wherein  $A_3$  has a formula selected from:

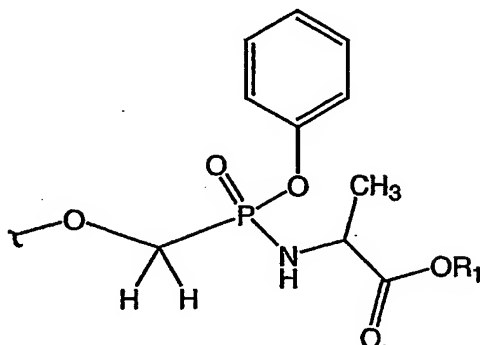


wherein  $m_1$  is 1, 2, 3, 4, 5, 6, 7 or 8, and the phenyl carbocycle is substituted with 0 to 3  $R_2$  groups.

10 128. The compound of claim 125 wherein  $A_3$  has a formula selected from:



129. The compound of claim 128 wherein A<sub>3</sub> has a formula selected from:



130. A method of inhibiting the activity of HIV protease comprising the step of  
5 contacting a sample suspected of containing HIV with a composition of claim 1.

131. The method of claim 130 wherein the HIV protease is *in vivo*.

132. A method for the treatment or prevention of the symptoms or effects of HIV  
10 infection in an animal which comprises administering to said animal a formulation comprising a therapeutically effective amount of a compound according to claim 1.

133. The method of claim 132 wherein the compound is formulated with a  
15 pharmaceutically acceptable carrier.

134. The use of a compound of claim 1 to prepare a medicament for treatment of  
AIDS.

135. The use of a compound of claim 3 to prepare a medicament for treatment of  
20 AIDS.

136. The method of claim 133 wherein the formulation further comprises a second  
active ingredient selected from a nucleotide reverse transcriptase inhibitor, a non-nucleoside  
reverse transcriptase inhibitor, an HIV protease inhibitor, and an HIV integrase inhibitor.

25

137. A process for preparing a compound of claim 1 wherein a compound comprising A<sup>3</sup> or a precursor to A<sup>3</sup> is reacted with an HIV protease inhibitor compound wherein the HIV protease inhibitor compound does not have a phosphonate group, whereby a compound of claim 1 is formed.

5

138. In an HIV protease inhibitor, the improvement comprising a substituent having a phosphonate or phosphonate prodrug.

139. The improved HIV protease inhibitor compound of claim 138 selected from:

10

a Saquinavir-like phosphonate protease inhibitor compound,

a Lopinavir-like phosphonate protease inhibitor compound,

a Ritonavir-like phosphonate protease inhibitor compound,

a Indinavir-like phosphonate protease inhibitor compound,

a Atazanavir-like phosphonate protease inhibitor compound,

15

a Nelfinavir-like phosphonate protease inhibitor compound,

a Tipranavir-like phosphonate protease inhibitor compound,

a Amprenavir-like phosphonate protease inhibitor compound,

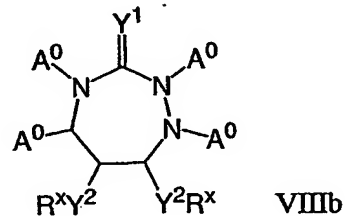
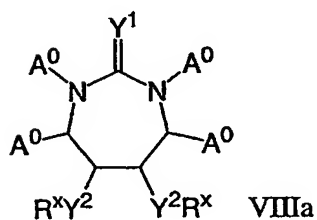
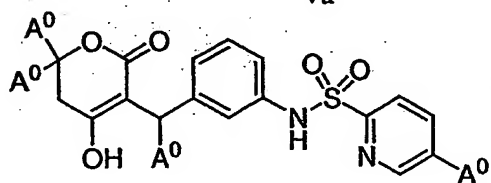
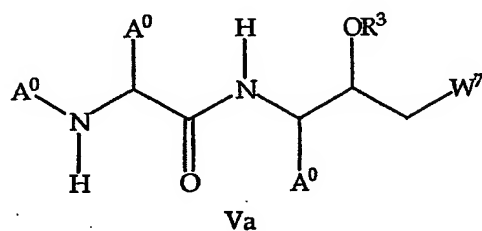
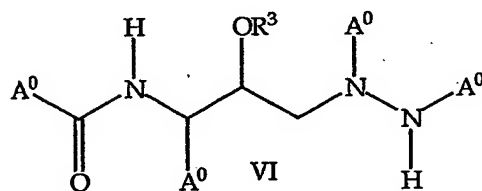
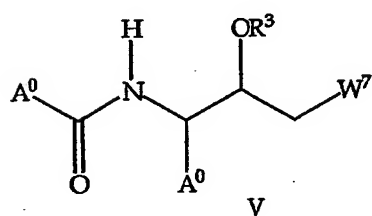
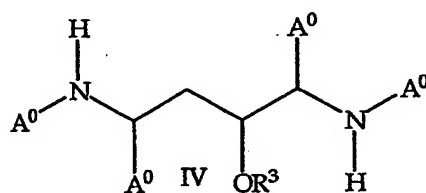
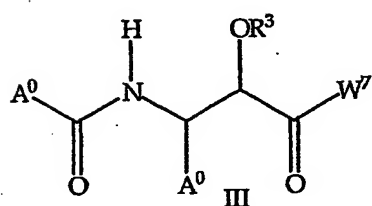
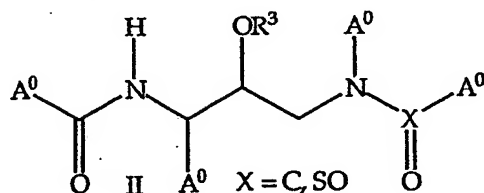
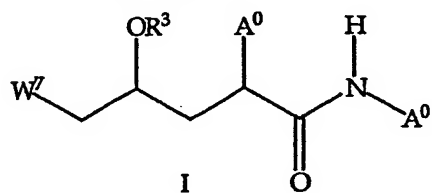
a KNI-like phosphonate protease inhibitor compound, and

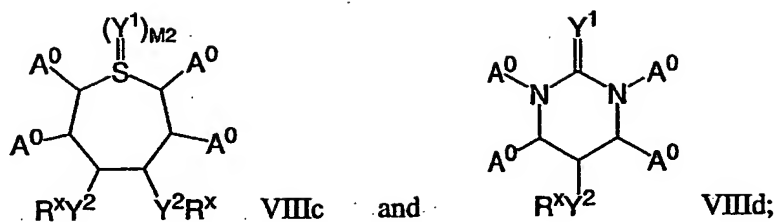
a Cyclic Carbonyl-like phosphonate protease inhibitor compound;

20

and pharmaceutically acceptable salts, hydrates, and formulations thereof.

140. The improved HIV protease inhibitor compound of claim 138 of the Formulas:



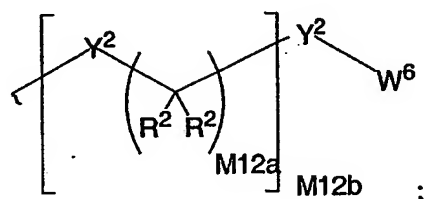


**wherein:**

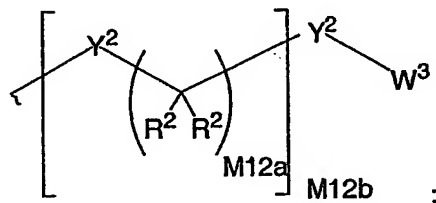
$A^0$  is  $A^1$ ,  $A^2$  or  $W^3$  with the proviso that the compound includes at least one  $A^1$ ;

5

**A<sup>1</sup> is:**

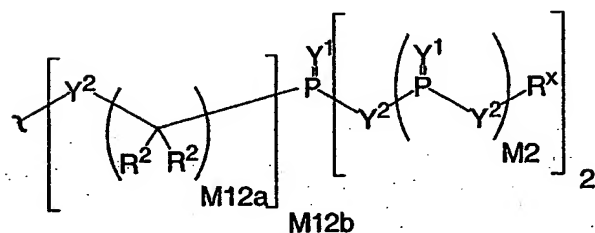


**A<sup>2</sup> is:**



10

**A<sup>3</sup> is:**



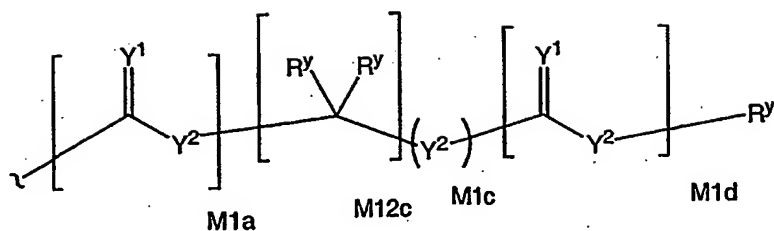
**Y<sup>1</sup>** is independently O, S, N(R<sup>x</sup>), N(O)(R<sup>x</sup>), N(OR<sup>x</sup>), N(O)(OR<sup>x</sup>), or N(N(R<sup>x</sup>)(R<sup>x</sup>));

**Y<sup>2</sup>** is independently a bond, O, N(R<sup>x</sup>), N(O)(R<sup>x</sup>), N(OR<sup>x</sup>), N(O)(OR<sup>x</sup>), N(N(R<sup>x</sup>)(R<sup>x</sup>)),

-S(O)<sub>M2</sub>-, or -S(O)<sub>M2</sub>-S(O)<sub>M2</sub>-;

15

**R<sup>x</sup> is independently H, R<sup>1</sup>, W<sup>3</sup>, a protecting group, or the formula:**



$\text{R}^{\text{Y}}$  is independently H,  $\text{W}^3$ ,  $\text{R}^2$  or a protecting group;

$\text{R}^1$  is independently H or an alkyl of 1 to 18 carbon atoms;

$\text{R}^2$  is independently H,  $\text{R}^1$ ,  $\text{R}^3$  or  $\text{R}^4$  wherein each  $\text{R}^4$  is independently substituted with 0 to 3  $\text{R}^3$  groups, or taken together at a carbon atom, two  $\text{R}^2$  groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3  $\text{R}^3$  groups;

$\text{R}^3$  is  $\text{R}^{3\text{a}}$ ,  $\text{R}^{3\text{b}}$ ,  $\text{R}^{3\text{c}}$  or  $\text{R}^{3\text{d}}$ , provided that when  $\text{R}^3$  is bound to a heteroatom, then  $\text{R}^3$  is  $\text{R}^{3\text{c}}$  or  $\text{R}^{3\text{d}}$ ;

$\text{R}^{3\text{a}}$  is F, Cl, Br, I, -CN,  $\text{N}_3$  or  $\text{-NO}_2$ ;

$\text{R}^{3\text{b}}$  is  $\text{Y}^1$ ;

$\text{R}^{3\text{c}}$  is  $\text{-R}^{\text{x}}$ ,  $\text{-N(R}^{\text{x}})(\text{R}^{\text{x}})$ ,  $\text{-SR}^{\text{x}}$ ,  $\text{-S(O)R}^{\text{x}}$ ,  $\text{-S(O)}_2\text{R}^{\text{x}}$ ,  $\text{-S(O)(OR}^{\text{x}})$ ,  $\text{-S(O)}_2(\text{OR}^{\text{x}})$ ,  $\text{-OC(Y}^1\text{)R}^{\text{x}}$ ,  $\text{-OC(Y}^1\text{)OR}^{\text{x}}$ ,  $\text{-OC(Y}^1\text{)(N(R}^{\text{x}})(\text{R}^{\text{x}}))}$ ,  $\text{-SC(Y}^1\text{)R}^{\text{x}}$ ,  $\text{-SC(Y}^1\text{)OR}^{\text{x}}$ ,  $\text{-SC(Y}^1\text{)(N(R}^{\text{x}})(\text{R}^{\text{x}}))}$ ,  $\text{-N(R}^{\text{x}})\text{C(Y}^1\text{)R}^{\text{x}}$ ,  $\text{-N(R}^{\text{x}})\text{C(Y}^1\text{)OR}^{\text{x}}$ , or  $\text{-N(R}^{\text{x}})\text{C(Y}^1\text{)(N(R}^{\text{x}})(\text{R}^{\text{x}}))}$ ;

$\text{R}^{3\text{d}}$  is  $\text{-C(Y}^1\text{)R}^{\text{x}}$ ,  $\text{-C(Y}^1\text{)OR}^{\text{x}}$  or  $\text{-C(Y}^1\text{)(N(R}^{\text{x}})(\text{R}^{\text{x}}))}$ ;

$\text{R}^4$  is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

$\text{R}^5$  is  $\text{R}^4$  wherein each  $\text{R}^4$  is substituted with 0 to 3  $\text{R}^3$  groups;

$\text{W}^3$  is  $\text{W}^4$  or  $\text{W}^5$ ;

$\text{W}^4$  is  $\text{R}^5$ ,  $\text{-C(Y}^1\text{)R}^5$ ,  $\text{-C(Y}^1\text{)W}^5$ ,  $\text{-SO}_2\text{R}^5$ , or  $\text{-SO}_2\text{W}^5$ ;

$\text{W}^5$  is carbocycle or heterocycle wherein  $\text{W}^5$  is independently substituted with 0 to 3  $\text{R}^2$  groups;

$\text{W}^6$  is  $\text{W}^3$  independently substituted with 1, 2, or 3  $\text{A}^3$  groups;

$\text{W}^7$  is a heterocycle bonded through a nitrogen atom of said heterocycle and independently substituted with 0, 1 or 2  $\text{A}^0$  groups;

$\text{M}2$  is 0, 1 or 2;

$\text{M}12\text{a}$  is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

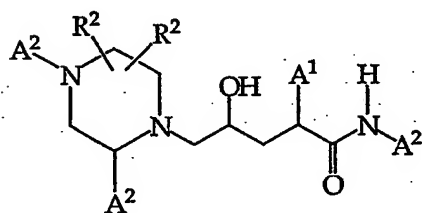
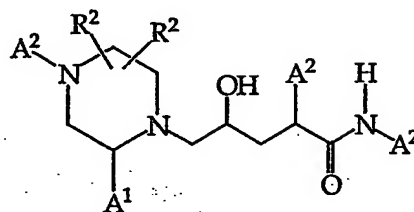
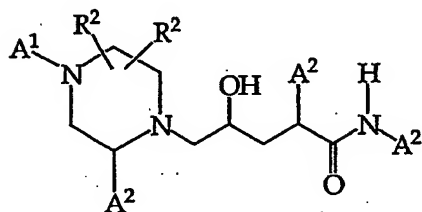
$\text{M}12\text{b}$  is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

$\text{M}1\text{a}$ ,  $\text{M}1\text{c}$ , and  $\text{M}1\text{d}$  are independently 0 or 1; and

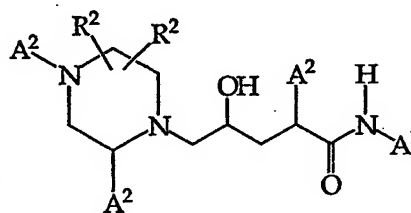


M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

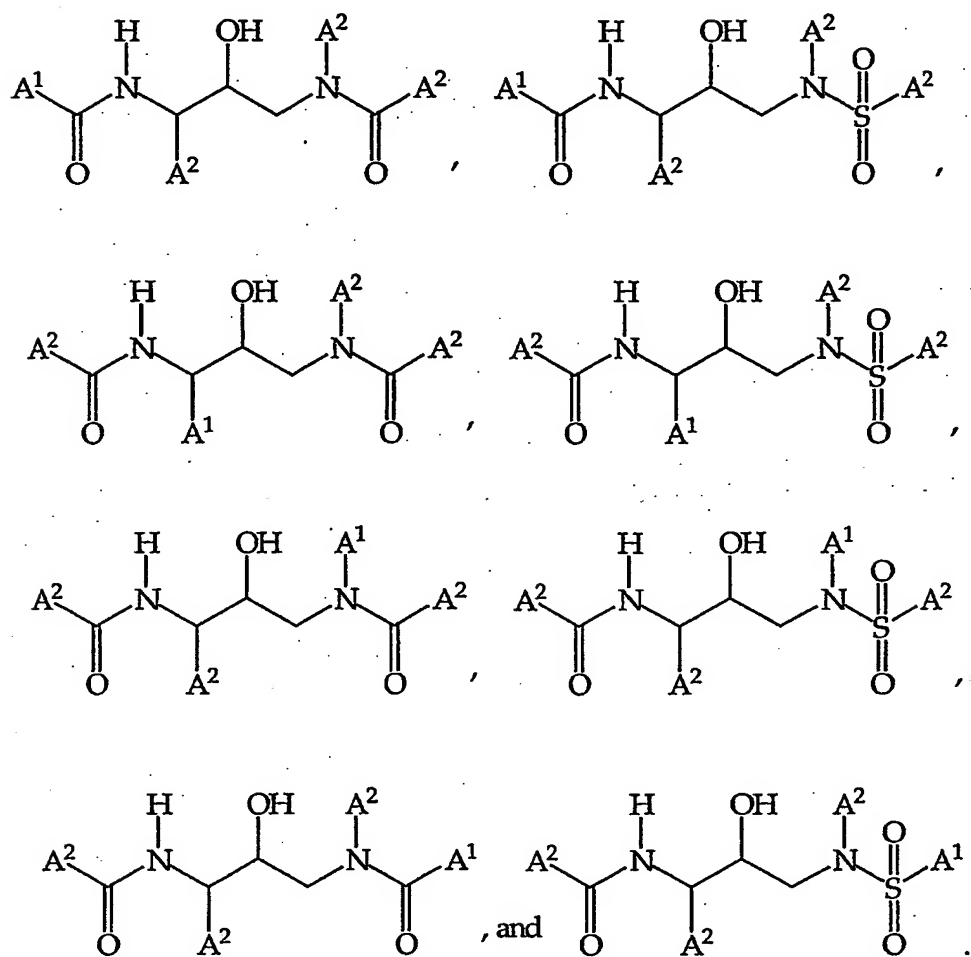
141. The improved HIV protease inhibitor compound of claim 140 of the Formulas:



, and

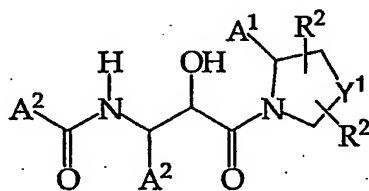
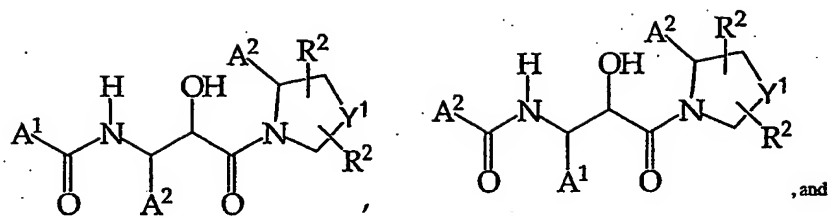


142. The improved HIV protease inhibitor compound of claim 140 of the Formulas:

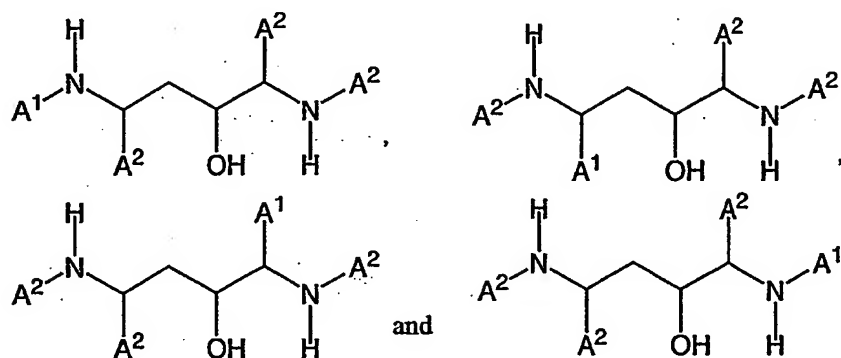


5

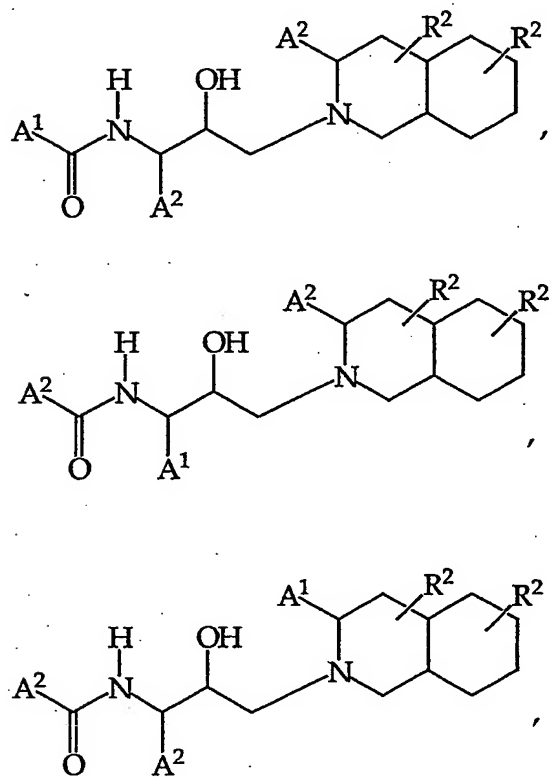
143. The improved HIV protease inhibitor compound of claim 140 of the Formulas:

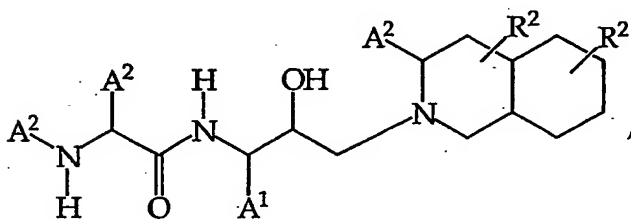
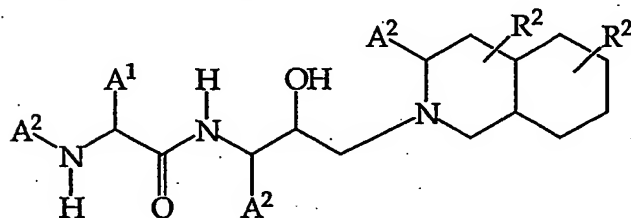
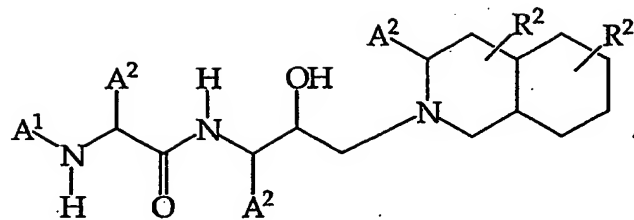


144. The improved HIV protease inhibitor compound of claim 140 of the Formulas:

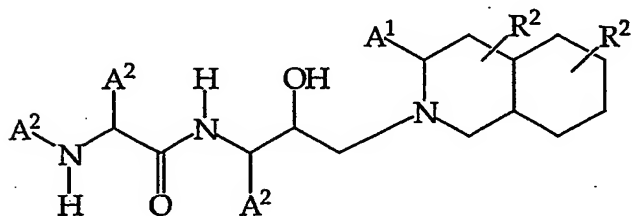


5 145. The improved HIV protease inhibitor compound of claim 140 of the Formulas:

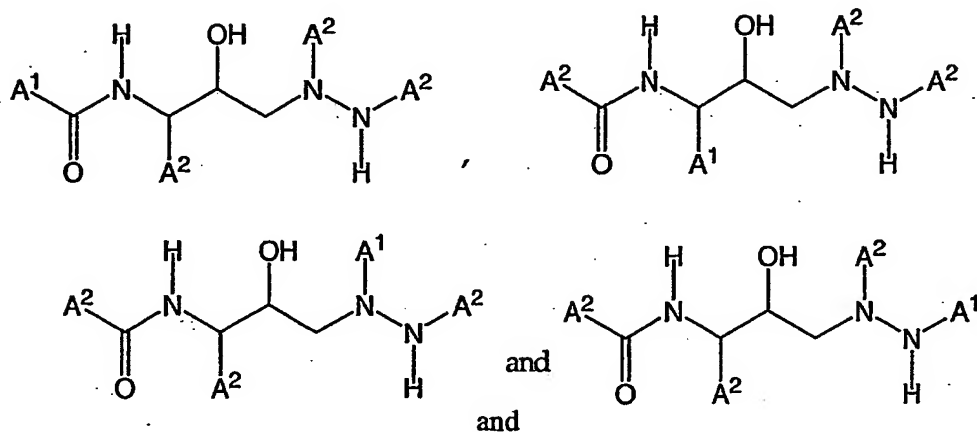




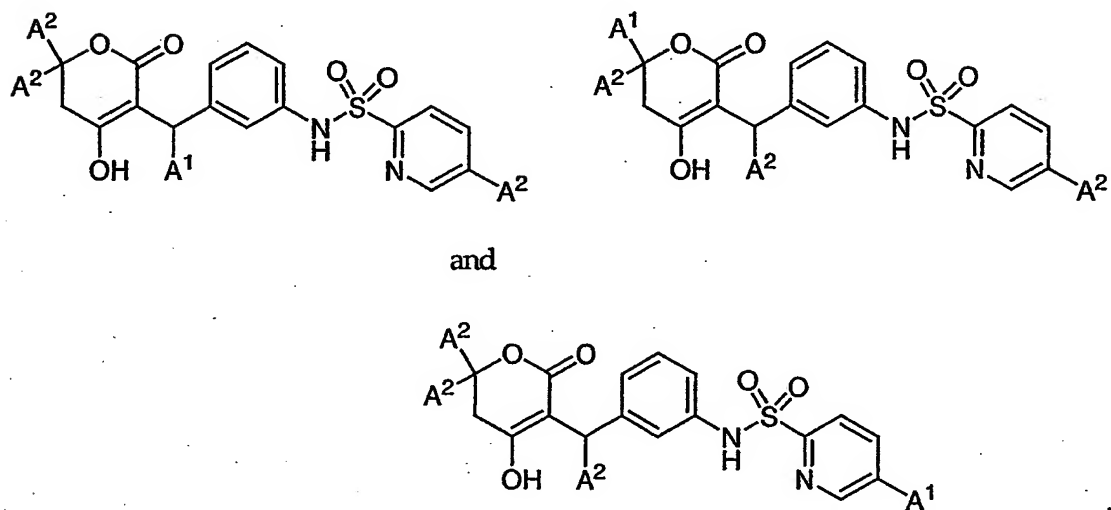
and



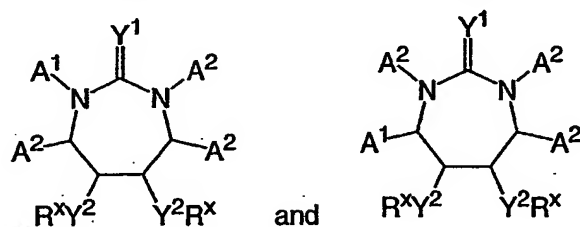
**146. The improved HIV protease inhibitor compound of claim 140 of the Formulas:**



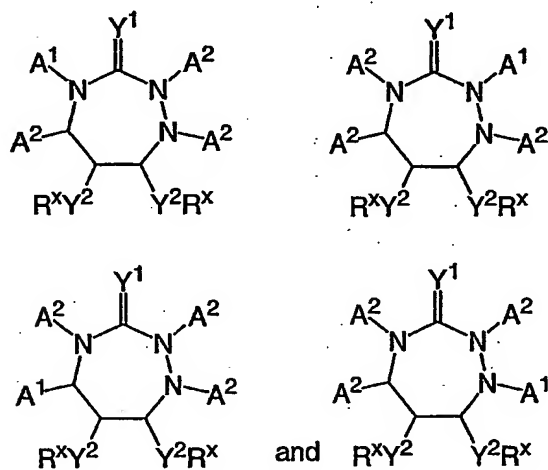
**147. The improved HIV protease inhibitor compound of claim 140 of the Formulas:**



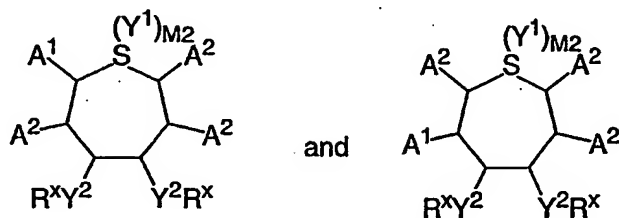
148. The improved HIV protease inhibitor compound of claim 140 of the Formulas:



149. The improved HIV protease inhibitor compound of claim 140 of the Formulas:

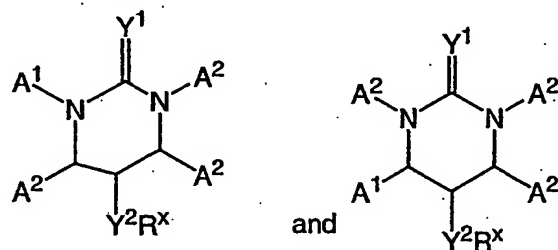


150. The improved HIV protease inhibitor compound of claim 140 of the Formulas:



5

151. The improved HIV protease inhibitor compound of claim 140 of the Formulas:

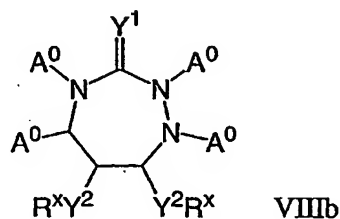
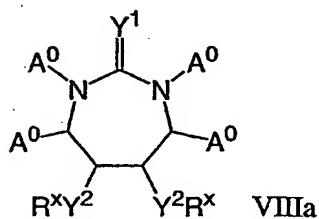
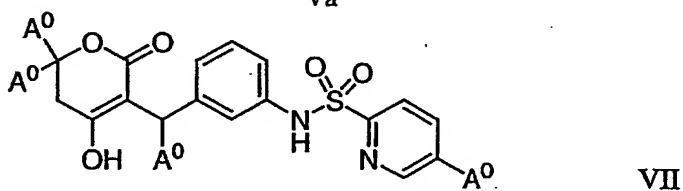
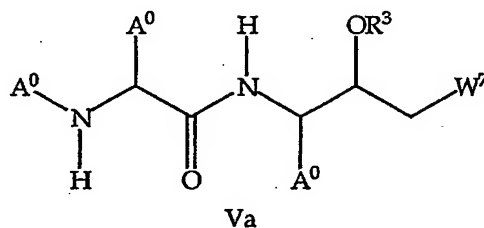
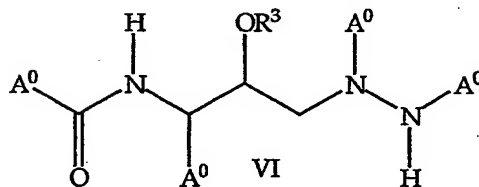
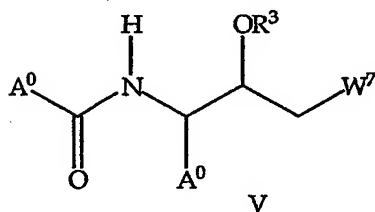
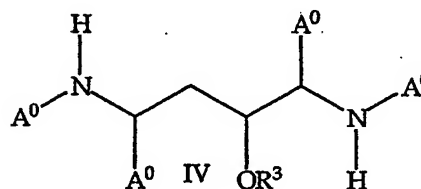
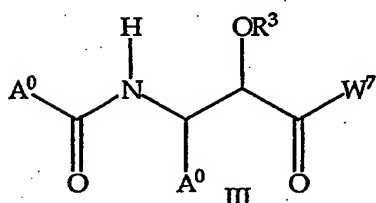
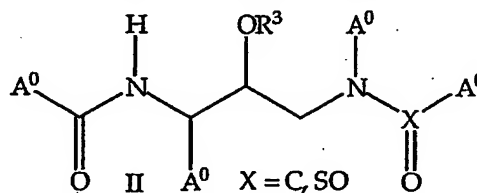
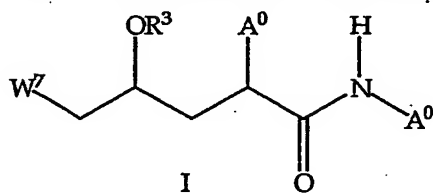


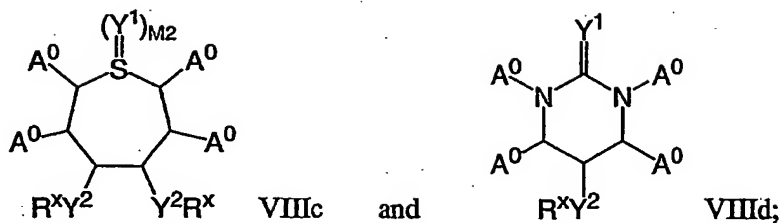


152. In an HIV protease inhibitor not containing a phosphonate or phosphonate prodrug, the improvement comprising a substituent having a phosphonate or phosphonate prodrug.

- 5           153. The improved HIV protease inhibitor compound of claim 152 selected from:  
a Saquinavir-like phosphonate protease inhibitor compound,  
a Lopinavir-like phosphonate protease inhibitor compound,  
a Ritonavir-like phosphonate protease inhibitor compound,  
a Indinavir-like phosphonate protease inhibitor compound,  
10          a Atazanavir-like phosphonate protease inhibitor compound,  
a Nelfinavir-like phosphonate protease inhibitor compound,  
a Tipranavir-like phosphonate protease inhibitor compound,  
a Amprenavir-like phosphonate protease inhibitor compound,  
a KNI-like phosphonate protease inhibitor compound, and  
15          a Cyclic Carbonyl-like phosphonate protease inhibitor compound;  
and pharmaceutically acceptable salts, hydrates, and formulations thereof.

154. The improved HIV protease inhibitor compound of claim 152 of the Formulas:

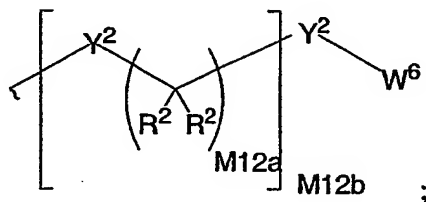




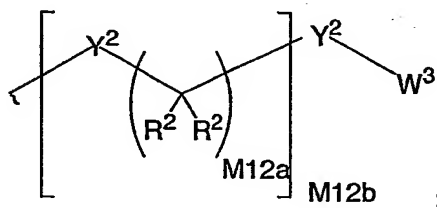
wherein:

$A^0$  is  $A^1$ ,  $A^2$  or  $W^3$  with the proviso that the compound includes at least one  $A^1$ ;

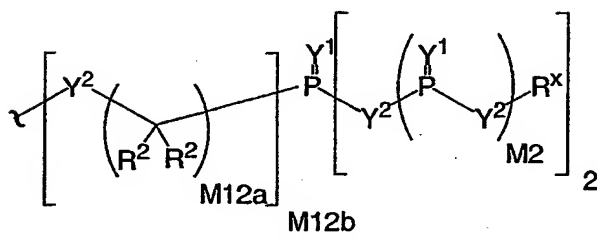
5  $A^1$  is:



$A^2$  is:



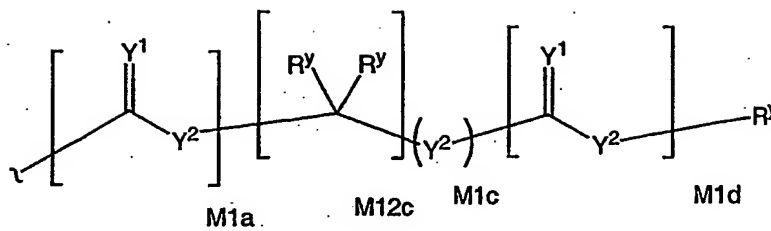
10  $A^3$  is:



$Y^1$  is independently O, S,  $N(R^x)$ ,  $N(O)(R^x)$ ,  $N(OR^x)$ ,  $N(O)(OR^x)$ , or  $N(N(R^x)(R^x))$ ;

$Y^2$  is independently a bond, O,  $N(R^x)$ ,  $N(O)(R^x)$ ,  $N(OR^x)$ ,  $N(O)(OR^x)$ ,  $N(N(R^x)(R^x))$ ,  $-S(O)_{M2}-$ , or  $-S(O)_{M2}-S(O)_{M2}-$ ;

15  $R^x$  is independently H,  $R^1$ ,  $W^3$ , a protecting group, or the formula:



$R^Y$  is independently H,  $W^3$ ,  $R^2$  or a protecting group;

$R^1$  is independently H or an alkyl of 1 to 18 carbon atoms;

$R^2$  is independently H,  $R^1$ ,  $R^3$  or  $R^4$  wherein each  $R^4$  is independently substituted with 0 to 3  $R^3$  groups, or taken together at a carbon atom, two  $R^2$  groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3  $R^3$  groups;

$R^3$  is  $R^{3a}$ ,  $R^{3b}$ ,  $R^{3c}$  or  $R^{3d}$ , provided that when  $R^3$  is bound to a heteroatom, then  $R^3$  is  $R^{3c}$  or  $R^{3d}$ ;

$R^{3a}$  is F, Cl, Br, I, -CN,  $N_3$  or -NO<sub>2</sub>;

$R^{3b}$  is  $Y^1$ ;

$R^{3c}$  is  $-R^x$ ,  $-N(R^x)(R^x)$ ,  $-SR^x$ ,  $-S(O)R^x$ ,  $-S(O)_2R^x$ ,  $-S(O)(OR^x)$ ,  $-S(O)_2(OR^x)$ ,  $-OC(Y^1)R^x$ ,  $-OC(Y^1)OR^x$ ,  $-OC(Y^1)(N(R^x)(R^x))$ ,  $-SC(Y^1)R^x$ ,  $-SC(Y^1)OR^x$ ,  $-SC(Y^1)(N(R^x)(R^x))$ ,  $-N(R^x)C(Y^1)R^x$ ,  $-N(R^x)C(Y^1)OR^x$ , or  $-N(R^x)C(Y^1)(N(R^x)(R^x))$ ;

$R^{3d}$  is  $-C(Y^1)R^x$ ,  $-C(Y^1)OR^x$  or  $-C(Y^1)(N(R^x)(R^x))$ ;

$R^4$  is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

$R^5$  is  $R^4$  wherein each  $R^4$  is substituted with 0 to 3  $R^3$  groups;

$W^3$  is  $W^4$  or  $W^5$ ;

$W^4$  is  $R^5$ ,  $-C(Y^1)R^5$ ,  $-C(Y^1)W^5$ ,  $-SO_2R^5$ , or  $-SO_2W^5$ ;

$W^5$  is carbocycle or heterocycle wherein  $W^5$  is independently substituted with 0 to 3  $R^2$  groups;

$W^6$  is  $W^3$  independently substituted with 1, 2, or 3  $A^3$  groups;

$W^7$  is a heterocycle bonded through a nitrogen atom of said heterocycle and independently substituted with 0, 1 or 2  $A^0$  groups;

M2 is 0, 1 or 2;

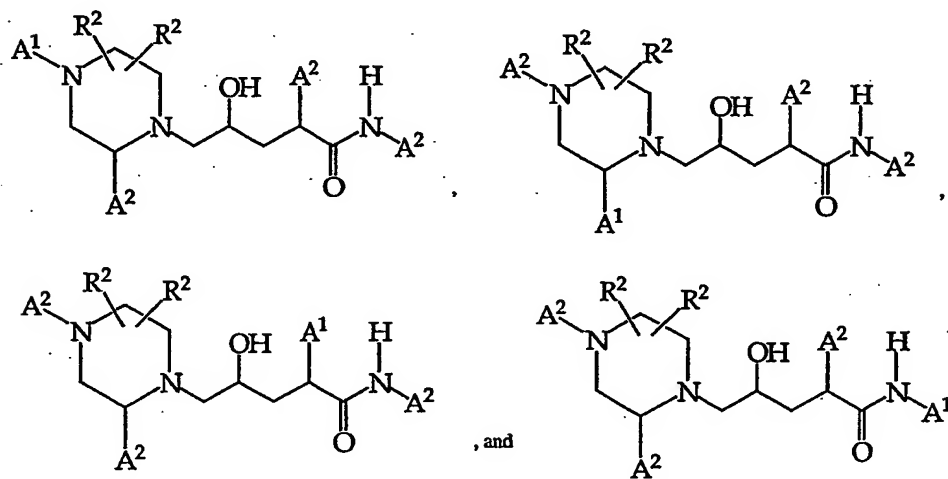
M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M1a, M1c, and M1d are independently 0 or 1; and

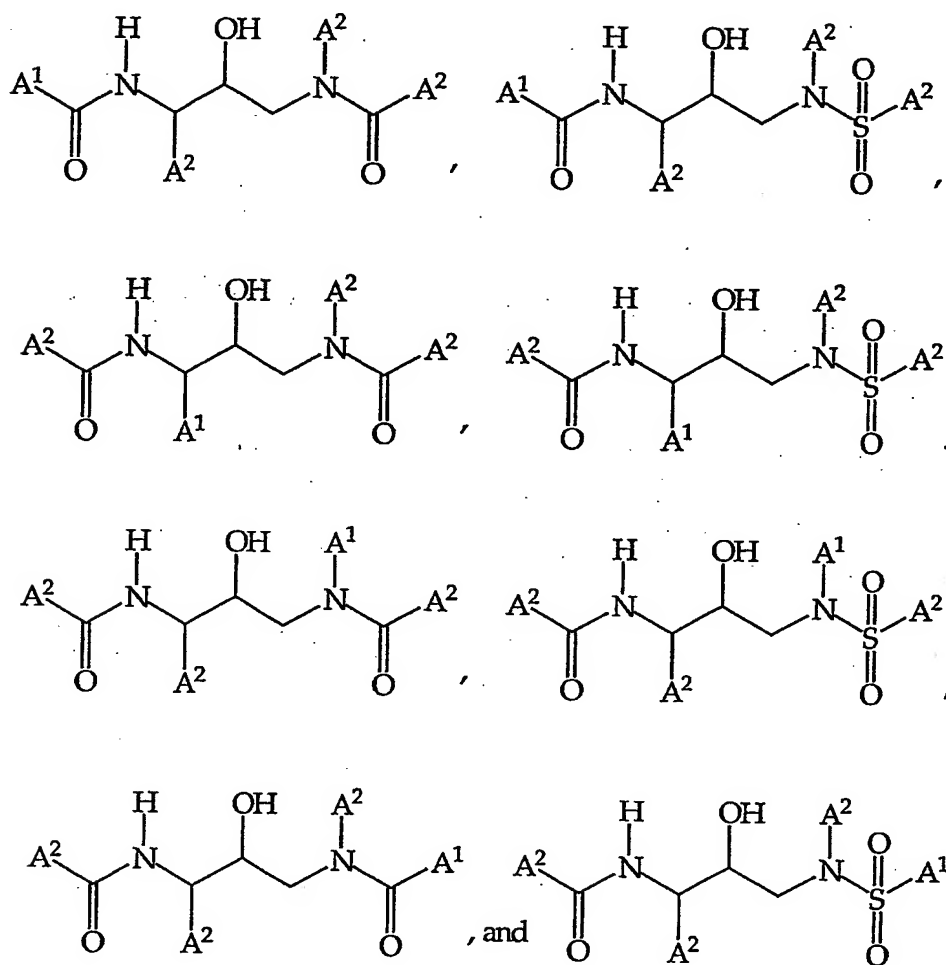
M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

155. The improved HIV protease inhibitor compound of claim 154 of the Formulas:



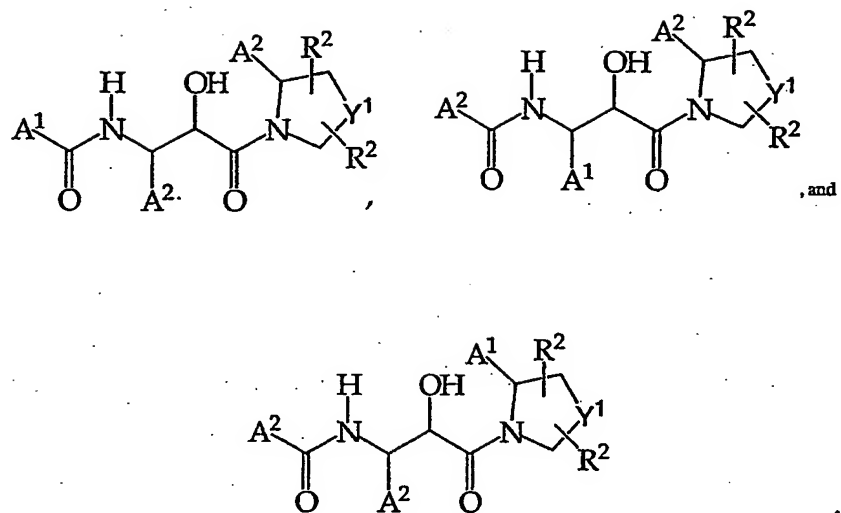
5

156. The improved HIV protease inhibitor compound of claim 154 of the Formulas:

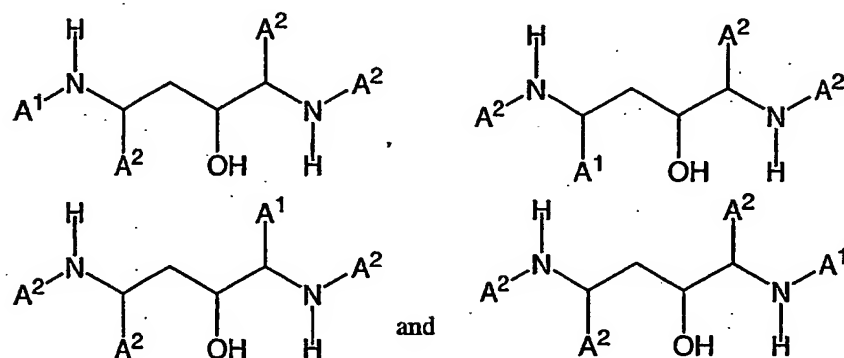


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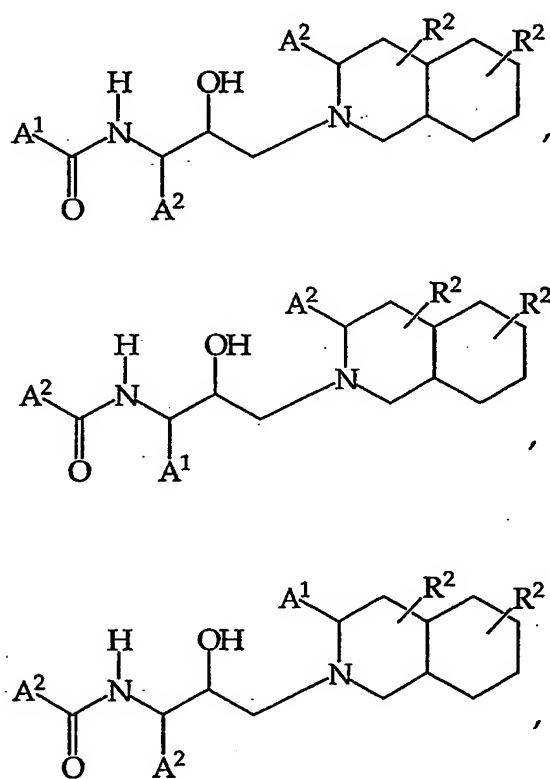
157. The improved HIV protease inhibitor compound of claim 154 of the Formulas:



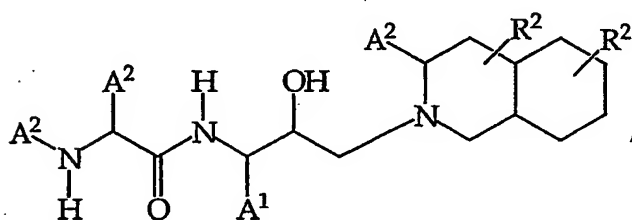
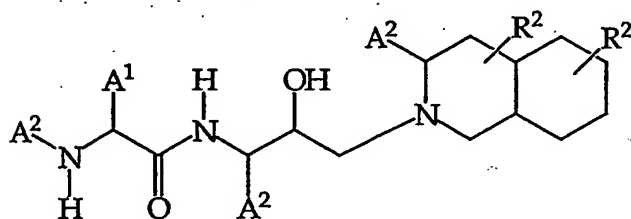
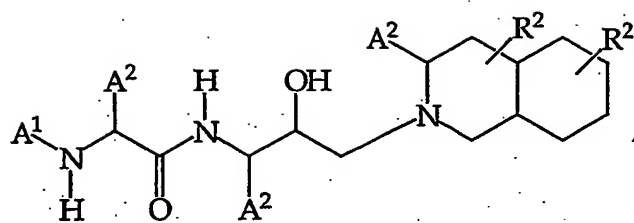
158. The improved HIV protease inhibitor compound of claim 154 of the Formulas:



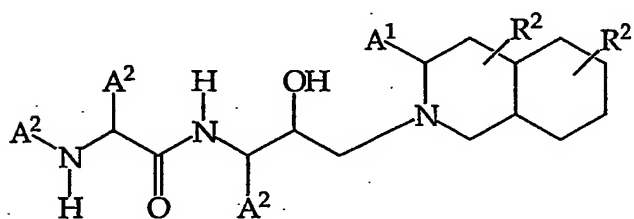
5 159. The improved HIV protease inhibitor compound of claim 154 of the Formulas:



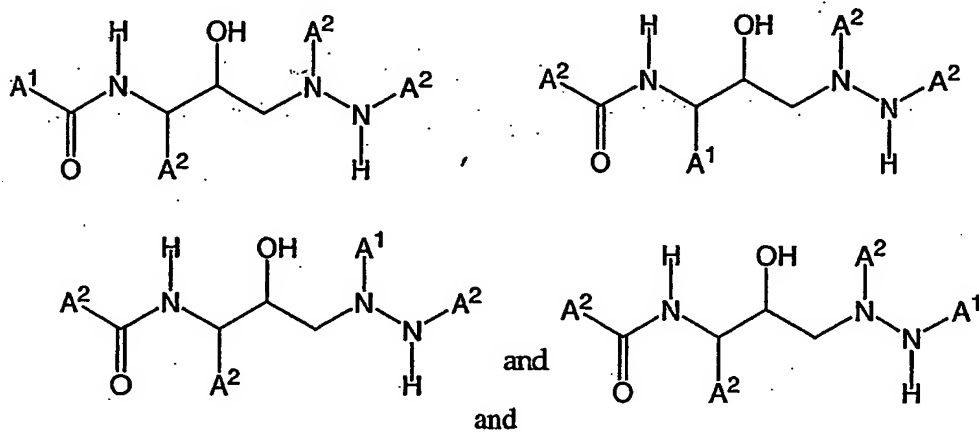




and

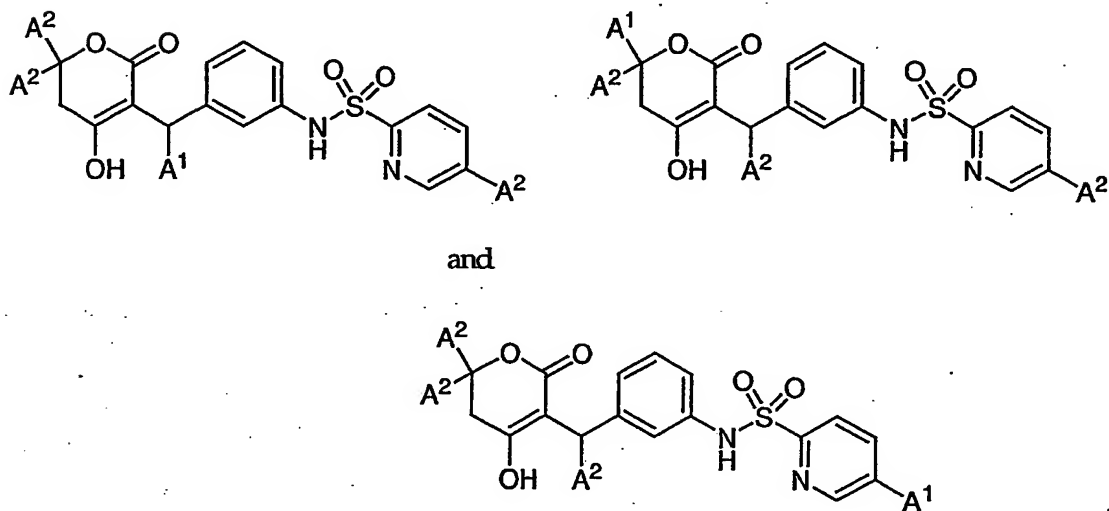


160. The improved HIV protease inhibitor compound of claim 154 of the Formulas:

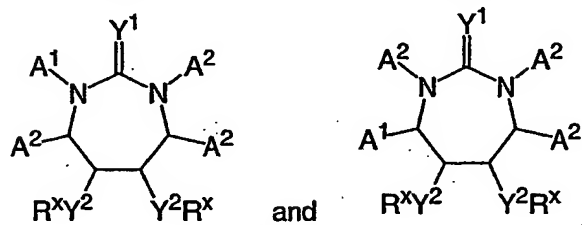


5

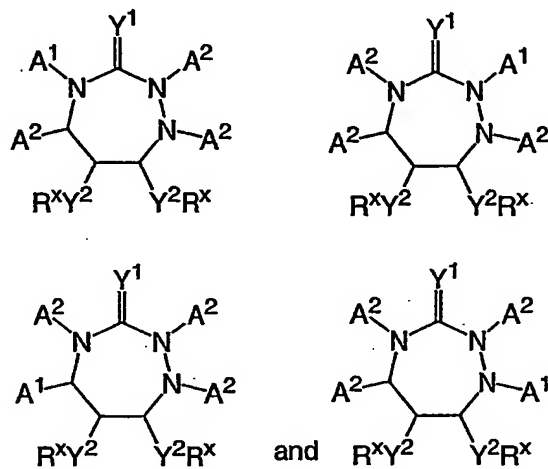
161. The improved HIV protease inhibitor compound of claim 154 of the Formulas:



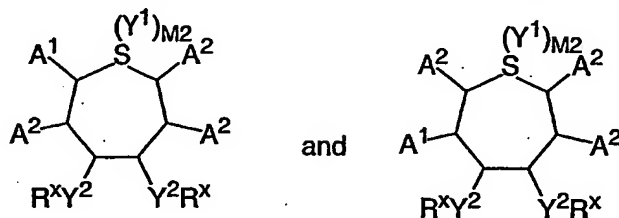
162. The improved HIV protease inhibitor compound of claim 154 of the Formulas:



163. The improved HIV protease inhibitor compound of claim 154 of the Formulas:

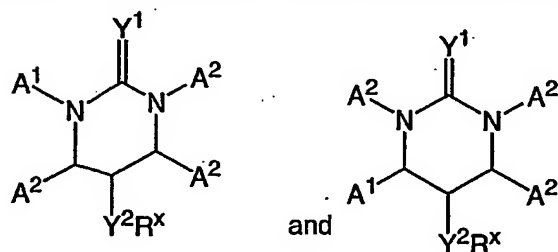


164. The improved HIV protease inhibitor compound of claim 154 of the Formulas:



5

165. The improved HIV protease inhibitor compound of claim 154 of the Formulas:



166. An MBF compound of Table 100.

167. A compound described herein.

5 168. A compound of Claim 167 described in the schemes or examples.

169. A method of making a compound described herein.

170. A method of Claim 169 described in the schemes or examples.

10

171. The use of a compound described here for treatment of HIV in humans.

172. The method of Claim 171 wherein the compound is described in the schemes or examples.

15

173 The use of a compound described here in the manufacture of a medicament.

174. The use of Claim 173 wherein the compound is described in the schemes or examples.

20

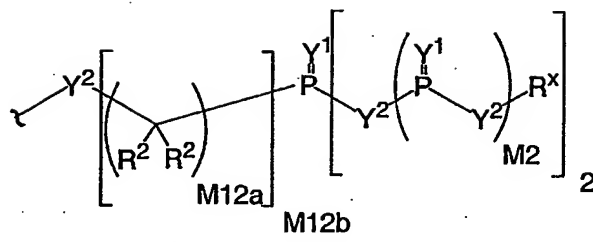
175. An HIV protease inhibitor compound capable of accumulating in human PBMCs.

25 176. The compound of Claim 175 further comprising a phosphonate or phosphonate prodrug.

177. The compound of Claim 176 wherein the phosphonate or phosphonate prodrug are of the formula A<sup>3</sup>:

30

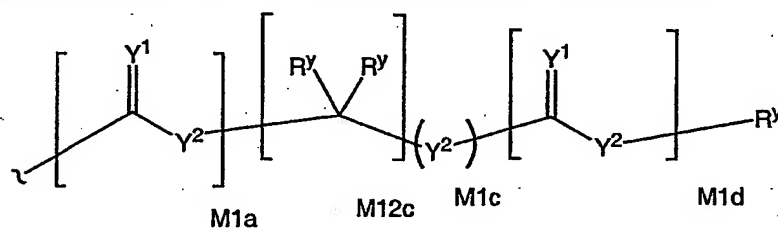
A<sup>3</sup> is:



$Y^1$  is independently O, S,  $N(R^x)$ ,  $N(O)(R^x)$ ,  $N(OR^x)$ ,  $N(O)(OR^x)$ , or  $N(N(R^x)(R^x))$ ;

$Y^2$  is independently a bond, O,  $N(R^x)$ ,  $N(O)(R^x)$ ,  $N(OR^x)$ ,  $N(O)(OR^x)$ ,  $N(N(R^x)(R^x))$ ,  $-S(O)_{M2}-$ , or  $-S(O)_{M2}-S(O)_{M2}-$ ;

5  $R^x$  is independently H,  $R^1$ ,  $W^3$ , a protecting group, or the formula:



$R^y$  is independently H,  $W^3$ ,  $R^2$  or a protecting group;

$R^1$  is independently H or an alkyl of 1 to 18 carbon atoms;

$R^2$  is independently H,  $R^1$ ,  $R^3$  or  $R^4$  wherein each  $R^4$  is independently substituted with  
10 0 to 3  $R^3$  groups;  
 $R^3$  is  $R^{3a}$ ,  $R^{3b}$ ,  $R^{3c}$  or  $R^{3d}$ , provided that when  $R^3$  is bound to a heteroatom, then  $R^3$  is  $R^{3c}$  or  $R^{3d}$ ;

$R^{3a}$  is F, Cl, Br, I, -CN,  $N_3$  or  $-NO_2$ ;

$R^{3b}$  is  $Y^1$ ;

15  $R^{3c}$  is  $-R^x$ ,  $-N(R^x)(R^x)$ ,  $-SR^x$ ,  $-S(O)R^x$ ,  $-S(O)_2R^x$ ,  $-S(O)(OR^x)$ ,  $-S(O)_2(OR^x)$ ,  $-OC(Y^1)R^x$ ,  $-OC(Y^1)OR^x$ ,  $-OC(Y^1)(N(R^x)(R^x))$ ,  $-SC(Y^1)R^x$ ,  $-SC(Y^1)OR^x$ ,  $-SC(Y^1)(N(R^x)(R^x))$ ,  $-N(R^x)C(Y^1)R^x$ ,  $-N(R^x)C(Y^1)OR^x$ , or  $-N(R^x)C(Y^1)(N(R^x)(R^x))$ ;

$R^{3d}$  is  $-C(Y^1)R^x$ ,  $-C(Y^1)OR^x$  or  $-C(Y^1)(N(R^x)(R^x))$ ;

$R^4$  is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of

20 2 to 18 carbon atoms;

$R^5$  is  $R^4$  wherein each  $R^4$  is substituted with 0 to 3  $R^3$  groups;

$W^3$  is  $W^4$  or  $W^5$ ;

$W^4$  is  $R^5$ ,  $-C(Y^1)R^5$ ,  $-C(Y^1)W^5$ ,  $-SO_2R^5$ , or  $-SO_2W^5$ ;

W<sup>5</sup> is carbocycle or heterocycle wherein W<sup>5</sup> is independently substituted with 0 to 3 R<sup>2</sup> groups;

M2 is 0, 1 or 2;

M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

5 M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M1a, M1c, and M1d are independently 0 or 1; and

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

10 178. The compound of Claim 177 wherein the intracellular half-life of the compound or an intracellular metabolite of the compound in human PBMCs is improved when compared to an analog of the compound not having the phosphonate or phosphonate prodrug.

15 179. The compound of Claim 178 wherein the half-life is improved by at least about 50%.

180. The compound of Claim 178 wherein the half-life is improved by at least about 100%.

20 181. The compound of Claim 178 wherein the intracellular half-life of a metabolite of the compound in human PBMCs is improved when compared to an analog of the compound not having the phosphonate or phosphonate prodrug.

25 182. The compound of Claim 181 wherein the half-life is improved by at least about 50%.

183. The compound of Claim 181 wherein the half-life is improved by at least about 100%.

30 184. The compound of Claim 181 wherein the half-life is improved by greater than 100%.

185. Use of a compound of the invention for the treatment of HIV infection.

186. Use of a compound of the invention in the manufacture of a medicament.

5 187. Use of a compound of the invention in the manufacture of a medicament for the treatment of disorders affecting white blood cells.

188. Method of treating a disorder affecting white blood cells, comprising:  
administering a compound of the invention to a patient in need of white-  
blood-cell targeting.

10 189. Method of targeting a compound to white blood cells, comprising:  
selecting a compound having a desired pharmaceutical activity and having a first structure;  
modifying said first structure by replacing one or more atom of said first structure  
15 with an organic substituent comprising a phosphonate group or incipient phosphonate group to provide a compound having a second structure.

20 190. A method of manufacturing a non-nucleoside compound having both selectivity for white blood cells and a desired pharmaceutical activity, comprising:  
chemically synthesizing a first molecule having a first structure containing a phosphonate or incipient phosphonate group, wherein said first structure differs from a second structure of a compound known to have said desired pharmaceutical activity by having at least one hydrogen atom of said second structure replaced by an organic substituent comprising a phosphonate group or incipient phosphonate group.

25 191. The method of claim 190, wherein said first molecule is synthesized by a series of chemical reactions in which a hydrogen of said second structure is replaced by said organic substituent.

30 192. The method of claim 190, wherein said first molecule is synthesized by a series of chemical reactions that never includes a molecule of said second structure.

35 193. Method of accumulating an HIV protease inhibitor inside a white blood cell, comprising:  
administering to a sample a composition comprising a compound of the invention.

40 194. The method of Claim 193 wherein said sample is a patient.

45 195. The method of claim 193, wherein said compound of the invention has a chemical structure A-B, wherein (a) a compound having structure A-H has HIV protease inhibitor activity and (b) substructure B comprises a phosphonate group or incipient phosphonate group.



196. Method of increasing half-life of a non-nucleoside compound having anti-retroviral activity, comprising:  
replacing at least one hydrogen atom or organic radical of said compound by an organic substituent comprising a phosphonate group or incipient phosphonate.

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197. Method of designing a drug having specificity for white blood cells for synthesis, comprising:

- 5       obtaining a first list of first compounds having a desired activity;  
      creating a second list of second compounds, each of said second compounds having a structure in which at least one hydrogen atom or organic radical of a compound of said first list has been replaced by an organic substituent comprising a phosphonate group or incipient phosphonate group; and  
10       selecting a synthetic pathway capable of producing some or all of said second compounds from available starting materials, thereby providing a third list of compounds and associated synthetic techniques.

198. Method of manufacturing a pharmaceutical composition having said specificity of claim 197, comprising:

- 15       synthesizing a compound selected from said third list using said associated synthetic technique; and  
      admixing said synthesized compound with a pharmaceutically acceptable carrier.

20       199. A composition produced by the method of claim 198.

200. Method for producing a pharmaceutical composition having specificity for white blood cells, comprising:

- 25       admixing a therapeutically effective amount of a compound of the invention with a pharmaceutically acceptable carrier.

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